Bacterial Concrete— A Laboratory Investigation

Sivva Hemanth Sai[1] and Chigullapally Mounika[2]

[1]Department of Civil Engineering, Nalla Narasimha Reddy Education Society's Group of Institutions

[2]Department of Civil Engineering, Vignana Bharathi Institute of Technology

E-mail: [1]hemanthsai.sivva@gmail.com; [2]mounika.chigullapally@vbithyd.ac.in

ABSTRACT: *Concrete is brittle by nature that has a tendency to develop cracks with the passage of time. It is the only construction material which satisfies the properties of strength and durability. The development of cracks induces problems on the reinforcement with the intrusion of salts, chlorides and water through these cracks. To counteract this problem, the concept of Bacterial Concrete can be used by which concrete heals itself, the micro cracks developed at the early stage which can also be called as a Self-Healing Concrete. From the various studies, it is observed that 10% replacement of fly ash with the cement in concrete production gives the better results. In this project work, Bacteria is prepared using Bacillus Subtilis, the culture which is laboratory developed in the institution using the raw bacteria. Along with the Bacterial Concrete, Fly ash of 10% is added as a replacement of cement and the concrete is produced. 5%, 10% and 15% of water is replaced with the developed bacteria and added to the flyash concrete. Laboratory tests viz., Compressive Strength Test and Split Tensile Test are carried out and the results are compared.*

Keywords: Bacillus Subtilis, Bacteria Culture, Cracks, Fly Ash Concrete Bacterial Concrete, Petri Dish.

1. INTRODUCTION

Concrete is the familiar material used for constructions in all the type of Civil Engineering works. Its strength and durability are the major factors for the consideration of concrete. This being a mixture of cement, aggregates and water is strong in resisting in compressive loads and weaker in tensile loads. As the age of the structure increases, due to many reasons like loads application and environmental hazards, concrete structure gets cracks. The limit of serviceability is affected due to these cracks formation. Apart from it, early cracks are developed in concrete due to improper curing, moisture entering into the concrete through voids, sulphates and chlorides present which adversely affect the durability of the concrete structure. These cracks formation in concrete structures can be healed themselves at the early stage of concrete production provided the proper curing and other preliminary works are done. This self healing concept which uses the bacteria helps the demand of repair and maintenance of concrete structures after ages. Along all the other agents for self healing, the bacteria which is environmental friendly and doesn't harm to the mankind is effective in use after research.

Calcium Carbonate which is produced after the bacteria gets in touch with the water heals the cracks at the early stage which doesn't need any repair. Bacterial Concrete or Self Healing Concrete is a biological product which produces limestone on the surface of concrete. Bacillus subtilis is the bacteria which are used in this study. The bacteria lives dormant in concrete for 200 years.

At the point when a concrete structure harms and water begins to enter in the splits present in it the microscopic organisms begins to benefit from the calcium lactate expending oxygen and changes over the solvent calcium lactate into insoluble limestone. The limestone framed in this way seals the breaks present.

It is like the procedure of how a cracked bone gets normally mended by osteoblast cells that mineralize to change bone. Utilization of oxygen in the bacterial change has an extra bit of leeway. Oxygen which turns into a basic component for the erosion of steel to happen is being utilized in the bacterial change. Consequently the toughness of steel in development gets higher.

Different Bacteria used in concrete are Bacillus pasteurii, Bacilli nesphaericus, Escherichia colli, Bacillus Subtilis, Bacillus cohnii, Bacillus pseodofirrius, Bacillus balodurais. Waste materials from various industries come as flyash that can be used for partial replacement of cement as it contains cementitious properties. It is recommended from literature survey that at 10% flyash can be used in partial replacement of cement. By adding flyash CO_2 emissions released from the concrete structure can be reduced to some extent. Flyash cement concrete is highly recommended these days and is in use in many of the present day constructions

2. LITERATURE REVIEW

1. Kunamineni Vijay, Meena Murmu, Shirish V.Deo, studied the types of bacteria used in concrete, the ways it can be applied as a healing agents, describes various properties of concrete which vary with the addition of bacteria. Micro-cracks are inherently present in concrete. This causes degradation of concrete leading to ingress of deleterious substances into concrete, resulting in deterioration of structures. Due to this concrete needs to be rehabilitated. To surmount these situations self-healing techniques are adopted. By the addition of urease engendering bacteria along with calcium source results in calcite precipitation in concrete. Bio-mineralization techniques give promising results in sealing the micro-cracks in concrete. The freshly composed micro-cracks can be sealed up by perpetual hydration process in concrete. The ureolytic bacteria which include Bacillus Pasteurii, Bacillus Subtilis which can engender urea are integrated along with the calcium source to seal the freshly composed micro cracks by $CaCO_3$ precipitation. For the amelioration of pore structure in concrete, the bacterial concentrations were optimized for better results. The literature shows that Encapsulation method will give better results than direct application method and also shows that the use of bacteria can increase the strength and durability properties of concrete.

2. Lagazo, Magil A., Noriesta, Carla Pamela D., Montecalvo, Marlou A., Roselle P. Alviar-Adviser demonstrated that the utilization of microorganisms-Bacillus Subtlis is productive for development a tough framework and life of the concrete structure has put forth for break control. In this paper, the system Microbiologically Induced Calcite Precipitation (MICP) is clinched. Utilization of Bacillus Subtilis alongside its nutrients which is the Sodium Bicarbonate ($NaHCo_3$), Ammonium Carbonate (NH_4Cl), Calcium Chloride Dehydrate ($CaCl_2$), and nutrient broth. The mixing proporton used is 1:2 ½: 5:0.45 along with 30 ml liquid form of Bacillus Subtilis with the cell concentration of 10^5 cells/ml. The strength of concrete mix is evaluated by conducting test on 150 mm × 150 mm × 150 mm cube for compressive strength test, 6 in × 12 in cylindrical mold for split tensile strength test, 21 in × 6 in × 6 in rectangular beams for flexural strength text and 3 in × 6 in for water absorption test, 3 specimens each test. All specimen utilized for recuperating is 4 in × 2 in × 2 in which is deliberately broken. The investigation demonstrates that there is a noteworthy increment in the quality of cement added with bacteria or bacterial concrete contrasted with conventional concrete and in this manner calcium carbonate precipitation is obvious following 3-4 weeks in small scale splits.
3. H.M. Jonkers Delft University of Technology, Faculty of Civil Engineering and Geosciences, presented the study that crack healing capacity of a specific bio-chemical additive, consisting of a mixture of viable but dormant bacteria and organic compounds packed in porous expanded clay particles, was investigated. Microscopic techniques in combination with permeability tests revealed that complete healing of cracks occurred in bacterial concrete and only partly in control concrete. The mechanism of crack healing in bacterial concrete presumably occurs through metabolic conversion of calcium lactate to calcium carbonate what results in crack-sealing. This biochemically mediated process resulted in efficient sealing of sub-millimeter sized (0.15 mm width) cracks. It is expected that further development of this new type of self-healing concrete will result in a more durable and moreover sustainable concrete which will be particularly suited for applications in wet environments where reinforcement corrosion tends to impede durability of traditional concrete constructions.

3. DEVELOPMENT OF THE CULTURE OF BACTERIA

Researchers with different bacteria proposed different bacterial concretes. The various bacteria used in the concrete are Bacillus pasteurii, Bacillus sphaericus, E.coli etc. In the present study an attempt was made by using the bacteria Bacillus subtillus. The main advantage of embedding bacteria in the concrete is that it can constantly precipitate calcite. This phenomenon is called microbiologically induced calcite precipitation (MICP). Calcium carbonate precipitation, a widespread phenomenon among bacteria, has been investigated due to its wide range of scientific and technological implications. Bacillus Subtillus is chosen as a medium in this thesis work, which is cultured in laboratory under proper conditions. Petri Dishes, Glass Tubes, Conical Flasks are sanitized using the

Autoclave machine in the laboratory. Raw Bacteria ***Bacillus SubtilIs*** is brought from the market.

Bacteria culture is developed by taking a small amount of the raw bacteria under the UV radiation zone. Food for bacteria is taken with different chemicals mixed with the distilled water which includes Beef extract powder- 1%, Peptone- 1%, Sodium chloride- 0.5%, Agar Agar Powder - 2% These mixture is stored in a 10ml glass tubes and raw bacteria of 1 ml is inserted into the glass tubes. These tubes are done again sterilization in the Autoclave machine at a pressure of 50 lb/in^2 by keeping the cotton plugs such that no liquid comes out it when high pressure is applied in the machine.

Figure 1: Sterilization of Petri Dishes and Conical Flask in Autoclave

Then, this liquid is applied on the petri dishes and waited until it becomes a solid (in the form of a wax). Streaks are drawn on it so that to identify the development of culture of the bacteria. These petri dishes are placed in the BOD incubator for 48 hours and the bacteria culture is developed after the removal of the petri dishes from the In Incubator. The developed bacteria can be seen with the naked eye which forms in a white color.

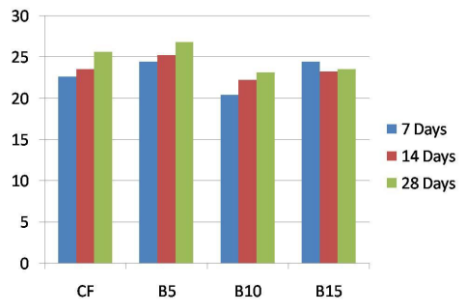
Figure 2: Transformation of Bacteria into the Petri Dishes for Development of Culture in the Presence of Ignition in UV Chamber

The developed culture is taken with a small amount using stirrer and placed in the required quantity of water that is used in the flyash bacterial concrete production. A concial flask is taken and distilled water poured into it and a small amount of bacteria is inoculated into the flask. This flask is again placed in the Autoclave for the proper mixing of bacteria into the water.

Concrete cubes and cylinders are casted as per the ratios mentioned above and are cured under proper conditions for the standard age. These specimens are tested under the compressive strength testing machine both for concrete compressive strength and split tensile strength test.

4. RESULTS AND DISCUSSIONS

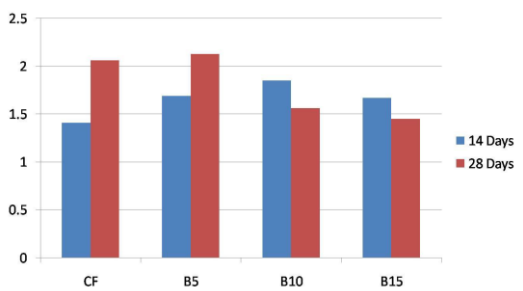
The Compressive Strength test is carried out for all the cubes which are casted and cured for the age of 7, 14 and 28 days.



Graph 1: Comparison of Compressive Strengths of the Cube Specimens

It is observed from the above graph that that a 5% replacement of bacteria with water in the concrete production has got better results when compared to the flyash concrete. However, it depends on the type of cracks developed in the cube. These results tells that at a very small percentage of bacteria, cracks are healed and if the bacteria is added more, no appreciable strength is identified.

The Split Tensile Strength test is carried out for all the cylinders which are casted and cured for the age of 14 and 28 days.



Graph 2: Comparison of Split Tensile Strengths of Cylindrical Specimens

From the above observations, the same B5% bacteria is giving the better results when compared to the B10 & B15 Bacteria Flyash Concrete.

5. CONCLUSIONS

From both the Tests, one can suggest that 5% of bacteria is enough to get the desired strength for concrete which indirectly tells us that the micro cracks are healed by itself. However, further the work can be extended for better results so that the materials can be used economically.

The following conclusions are observed in this research work:

1. By using flyash in the cement as partial replacement for producing bacterial flyash concrete CO_2 emissions that are released from the concrete can be stopped to little extent.
2. With a very small amount of raw bacteria, culture of bacteria can be developed which can be used for the concrete production that requires a skilled workers at site.
3. At 5% of bacteria the results are appreciable, further the work can be extended for 1%, 2%, 3% & 4% of bacteria.
4. The durability characteristics can be studied further using the percentage of bacteria used.

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Study of Bacterial Concrete Using SEM

Sivva Hemanth Sai[1], Chigullapally Mounika[2], P. Satish Kumar[3]

[1]Assistant Professor, Nalla Narasimha Reddy Education Society's Group of Institutions, Hyderabad.
[2]Assistant Professor, Vignana Bharathi Institute of Technology, Hyderabad.
[3]Assistant Professor, Nalla Narasimha Reddy Education Society's Group of Institutions, Hyderabad.
Email: hemanthsai.sivva@gmail.com[1], mounika.chigullapally@vbithyd.ac.in[2], satish.polkampally@gmail.com[3]

ABSTRACT

Concrete is brittle in nature, has tendency to get cracks at any stage of construction due to faulty materials, improper construction techniques, shrinkage, loads, etc.. To counteract the formation of cracks at early stage novel technique is under research, i.e., bacterial concrete which has the tendency to heal the cracks formed in the concrete by the formation of calcium lactate when bacteria is added to the concrete as a replacement of water which is called as MICP technique. Calcium Lactate is formed in the micro cracks and it helps the concrete to resist the cracks from widening. In this paper, Scanning Electron Microscopy (SEM) is performed for a concrete sample that is cured in water to visualize its formation and properties of bacterial concrete can be studied.

Key Words: *Cracks, Scanning Electron Microscopy, Bacterial Concrete, MICP Technique*

1. Introduction

Concrete is the familiar material used for constructions in all the type of civil engineering works. Its strength and durability are the major factors for the consideration of concrete. This being a mixture of cement, aggregates and water is strong in resisting in compressive loads and weaker in tensile loads. As the age of the structure increases, due to many reasons like loads application and environmental hazards, concrete structure gets cracks. The limit of serviceability is affected due to these cracks formation. Apart from it, early cracks are developed in concrete due to improper curing, moisture entering into the concrete through voids, sulphates and chlorides present which adversely affect the durability of the concrete structure. These cracks formation in concrete structures can be healed themselves at the early stage of concrete production provided the proper curing and other preliminary works are done. This self healing concept which uses the bacteria helps the demand of repair and maintenance of concrete structures after ages. Along all the other agents for self healing, the bacteria which is environmental friendly and doesn't harm to the mankind is effective in use after research. Calcium Carbonate which is produced after the bacteria gets in touch with the water heals the cracks at the early stage which doesn't need any repair. Bacterial Concrete or Self Healing Concrete is a biological product which produces limestone on the surface of concrete. Bacillus subtillus is the bacteria which are used in this study. The bacteria lives dormant in concrete for 200 years.

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At the point when a concrete structure harms and water begins to enter in the splits present in it the microscopic organisms begins to benefit from the calcium lactate expending oxygen and changes over the solvent calcium lactate into insoluble limestone. The limestone framed in this way seals the breaks present. It is like the procedure of how a cracked bone gets normally mended by osteoblast cells that mineralize to change bone. Utilization of oxygen in the bacterial change has an extra bit of leeway. Oxygen which turns into a basic component for the erosion of steel to happen is being utilized in the bacterial change. Consequently the toughness of steel in development gets higher.

Different Bacteria used in concrete are Bacillus pasteurii, Bacilli nesphaericus, Escherichia colli, Bacillus Subtilis, Bacillus cohnii, Bacillus pseodofirrius, Bacillus balodurais. Waste materials from various industries come as flyash that can be used for partial replacement of cement as it contains cementitious properties. It is recommended from literature survey that at 10% flyash can be used in partial replacement of cement. By adding flyash CO_2 emissions released from the concrete structure can be reduced to some extent. Flyash cement concrete is highly recommended these days and is in use in many of the present day constructions

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3. Development of the culture of bacteria

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Bacteria culture is developed by taking a small amount of the raw bacteria under the UV radiation zone. Food for bacteria is taken with different chemicals mixed with the distilled water which includes Beef extract powder- 1%, Peptone- 1%, Sodium chloride- 0.5%, Agar Agar Powder - 2%. These mixture is stored in a 10ml glass tubes and raw bacteria of 1 ml is inserted into the glass tubes. These tubes are done again sterilization in the Autoclave machine at a pressure

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Then, this liquid is applied on the petri dishes and waited until it becomes a solid (in the form of a wax). Streaks are drawn on it so that to identify the development of culture of the bacteria. These petri dishes are placed in the BOD incubator for 48 hours and the bacteria culture is developed after the removal of the petri dishes from the In Incubator. The developed bacteria can be seen with the naked eye which forms in a white color.

Fig 2. Transformation of bacteria into the petri dishes for development of culture in the presence of ignition in UV Chamber

The developed culture is taken with a small amount using stirrer and placed in the required quantity of water that is used in the flyash bacterial concrete production. A concial flask is taken and distilled water poured into it and a small amount of bacteria is inoculated into the flask. This flask is again placed in the Autoclave for the proper mixing of bacteria into the water.

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Concrete cubes and cylinders are casted as per the ratios mentioned above and are cured under proper conditions for the standard age. These specimens are tested under the compressive strength testing machine both for concrete compressive strength and split tensile strength test.

4. Scanning Electron Microscopy

Scanning electron microscopy (SEM) images are used to evaluate the microstructure of the concrete with a specified magnification for a sample of concrete. In these images, one can identify the crack that is healed after the crack formation. In the present study, sample of different scale bars are captured and studied for different features. The sample taken here is the bacteria with 5% replacement of water.

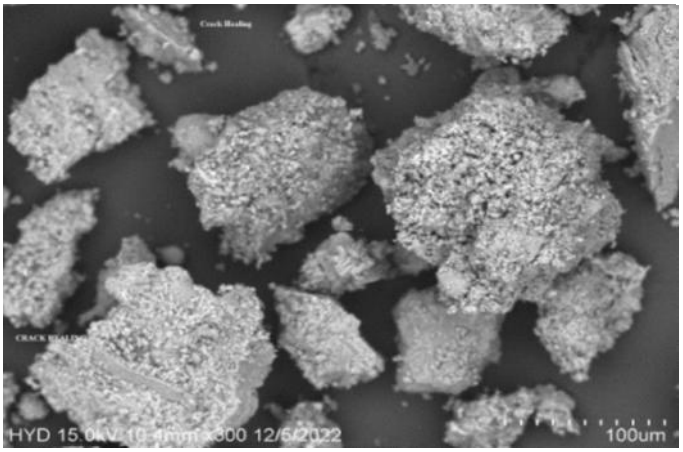

Fig 3 shows the SEM of 100 um scale bar of bacterial concrete in which crack healed by itself by the formation of Calcium Lactate

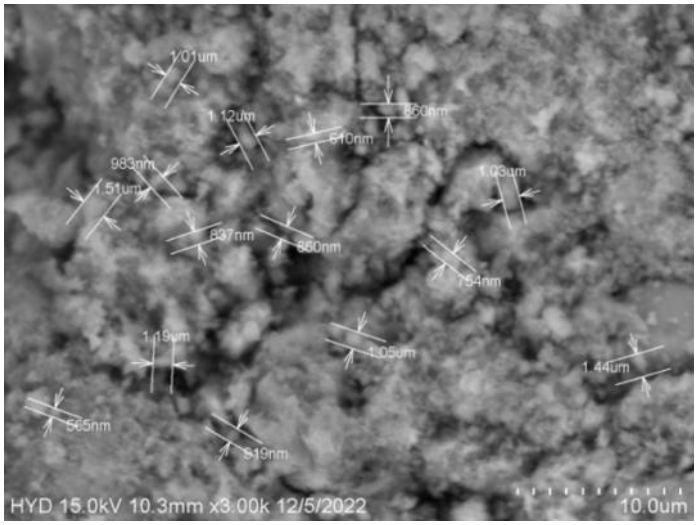

Fig 4 shows the SEM of 10.0 um scale bar of bacterial concrete

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In the present study, using SEM the formation of calcium lactate can be observed. The crack formed is healed by itself by MICP technique is observed.

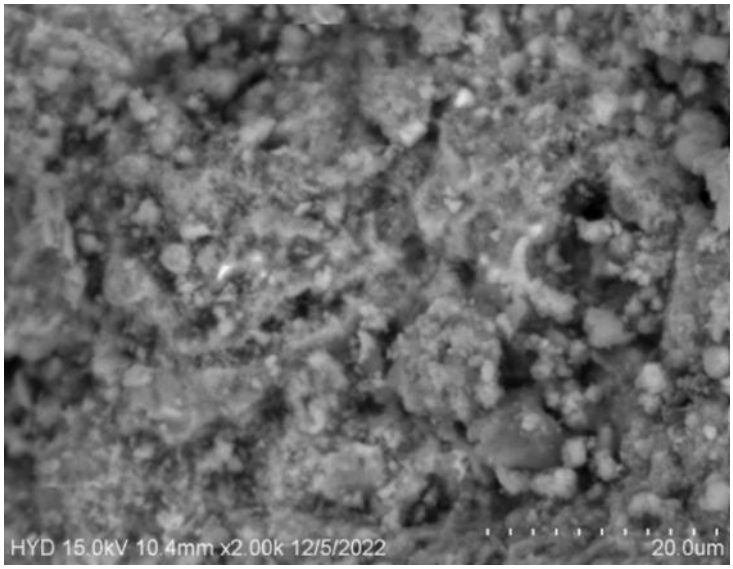
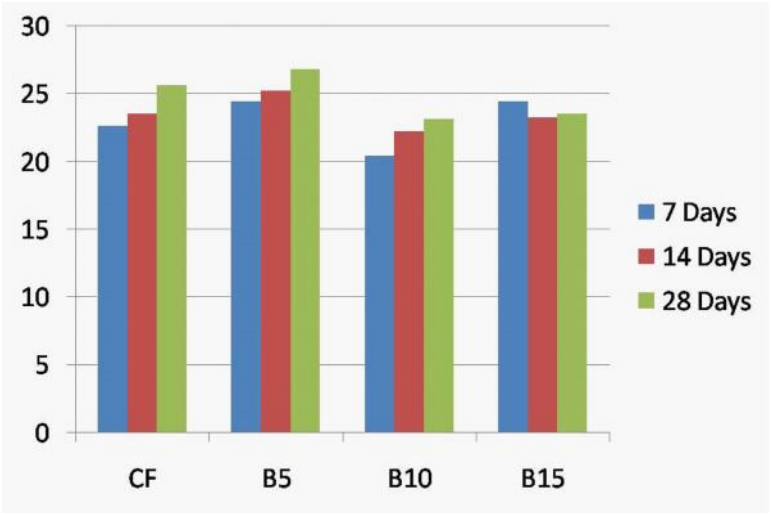


Fig 4 shows the SEM of 20.0 um scale bar of bacterial concrete

5. Results and Discussions

The Compressive Strength test is carried out for all the cubes which are casted and cured for the age of 7, 14 and 28 days.



Graph 1. Comparison of Compressive Strengths of the cube specimens

It is observed from the above graph that that a 5% replacement of bacteria with water in the concrete production has got better results when compared to the flyash concrete. However, it

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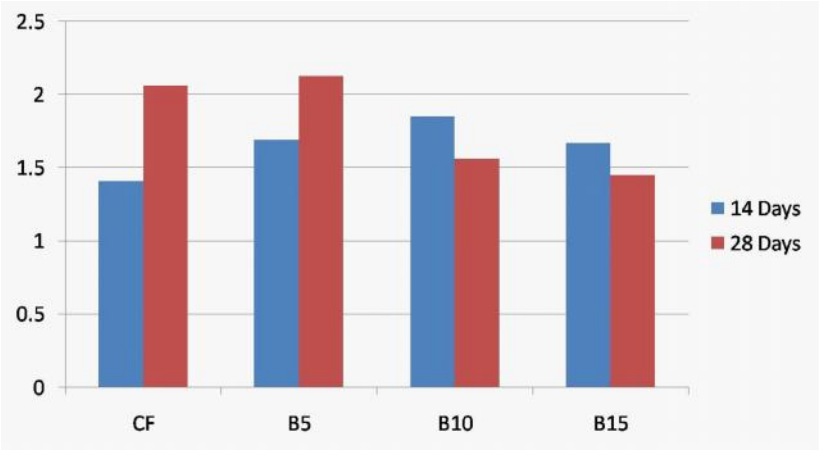
depends on the type of cracks developed in the cube. These results tells that at a very small percentage of bacteria, cracks are healed and if the bacteria is added more, no appreciable strength is identified.

The Split Tensile Strength test is carried out for all the cylinders which are casted and cured for the age of 14 and 28 days.



Graph 2.Comparison of Split Tensile Strengths of Cylindrical Specimens

From the above observations, the same B5% bacteria is giving the better results when compared to the B10 & B15 Bacteria Flyash Concrete.

V. CONCLUSIONS

From both the Tests, one can suggest that 5% of bacteria is enough to get the desired strength for concrete which indirectly tells us that the micro cracks are healed by itself. However, further the work can be extended for better results so that the materials can be used economically.

The following conclusions are observed in this research work:

1. By using flyash in the cement as partial replacement for producing bacterial flyash concrete CO_2 emissions that are released from the concrete can be stopped to little extent.
2. With a very small amount of raw bacteria, culture of bacteria can be developed which can be used for the concrete production that requires a skilled workers at site.
3. At 5% of bacteria the results are appreciable, further the work can be extended for 1%, 2%, 3% & 4% of bacteria.
4. SEM analysis can be done for more number of samples to get an optimized value.
5. The durability characteristics can be studied further using the percentage of bacteria used.

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Compressive strength of FRC utilizing ANN model

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Compressive Strength of FRC Utilizing ANN Model

Syed Anisuddin[1a], Hima BinduVarikola[1], Srikanth Gollapelli[1]

EkasilaSangam[1], VLSBanu[1], Hemanth Sai[2]

[1]*Civil Engineering Department, Lords Institute of Engineering & Technology, Hyderabad,Telangana,India.500091*
[2]*Civil Engineering Department, Nalla Narasimha Reddy Educational Society Group of Institutions, Hyderabad, Telangana, India.*

[a)]Corresponding author: "syedaneesuddin@lords.ac.in"

Abstract: In this paper, ANN has been applied to estimate the compressive strength of Fiber Reinforced Concrete. Nails have been used as fibers and its effects on the strength have been studied and compared. Study was carried out on cubes of standard size of FRC concrete with different mixing proportions and w/c ratios. The results obtained that for mix proportion (1:1.5:3) with 12% of fiber and an optimum w/c ratio of 0.46, also it is observed that less percent of large sized nails yielded high compressive strength. Whereas, for a mix proportion of (1:2:4) with 20% fiber, theoptimum w/c ratio was 0.55. Also, it is found that larger size of nails with less percent has yielded into high compressive strength and with the increase in percentage of fiber had decreased its strength.

Keywords: Fiber Reinforced Concrete (FRC), Compressive Strength, Aspect, W/C ratio, Artificial Neural Network (ANN) and Back Propagation Network (BPN).

INTRODUCTION

Materials like steel, plastic, glass, carbon and natural materials in different shapes and size are used to make this material which acts as a reinforcing material, and also helps to shift load to the micro cracks internally. FRC has been successfully accomplished and used in recent times, some of them include in construction due to its flexural-tensile strength, resistance to spitting, impact resistance, and good permeability and frost resistance. A numerical parameter describing the fiber is its aspect ratio, which is defined as the fiber length, divided by an equivalent fiber diameter [L/d].

A computational tool that tries to simulate the architecture and internal features of the nervous system and human brain is called Artificial Neural Network (ANN). A non– linear system having consisted of a high number of interconnected processing units, nodes or artificial neurons is called a neural network. Each input signal has the associated weight value (wi) to which it is multiplied by and summed at a neuron. To generate a level of activity for the neuron the result is put through an activation function. The output of the neuron is this activity. The connection pattern and weight value at each link are determined and are used to train the neural network. Learning from the training set and by applying for certain learning rule is used to accomplish this process. Inputs that are not including in the training set can be generated using this trained network.

In this study a training algorithm to assume the confined ultimate compressive strength of FRC based onconcrete mix proportions using nails as fibers has been formulated. Back propagation neural network (BPN) was built, tutored, and tested using data of concrete mix proportions and the estimated results were verified by laboratory testing. ANN model based on MATLAB was attempted in order to investigate the effects of different parameters on the behavior and compressive strength of this FRC.

LITERATURE REVIEW

Anisuddin had analyzed a transportation model utilizing ANN and BPN for estimating transit demand forHyderabad City. The model was run successfully to plan the alignment of the metro rail transit in accordance with the patronage (AnisuddinSyed,2006).

Newman et al., have discussed about the various aspects of Concrete and its properties (John Newman andBanSengChoo, 2003).

Panagiotis G. Asteris & Vaseilios G. Mokos had studied on the Concrete compressive strength using artificial neural networks. This project work studies over the prediction of compression strength of the given concrete specimen with the help of the Artificial Neural Networks.

Kim et al., applied the ANN model for estimation of Concrete strength and evaluated the correlation between the test results with that of forecasted one (Kim, J., Kie,D, Feng,M., and Yazdani,F., 2004).

Oretal, et al, carried out the Neural Network Modeling for Confined Compressive Strength and Strain of CircularConcrete Columns. They also reported that error analysis for the projected and actual values (Oretal, A., andKawashima, K. 2003).

A. Jain, Sanjeev Jhaand Mis applied the ANN on concrete and brought the actual compressive strengths of the given Fiber reinforced concrete and the exact Mix proportions of the concrete specimen.

EXPERIMENTAL WORK

In the experimental work of this study, 48 cubic were tested with 7 days and 28 days ages. The mixingproportion used were (1:1.5:3) and (1:2:4). The w/c ratio is taken between 0.40–0.55. The fibers used are nails with1"and1.5"size with adding ratiosof0-20%of the cement weight

NEURAL NETWORKS

MATLAB Neural Network Toolbox" was employed to investigate the compressive strength of FRC. A BPN was used in order to obtain the relationship between input parameters and output parameters. Trial–and–error method is used the configuration and train the neural networks because of the undetermined parameters as the number of nodes the number of training patterns, in the hidden layer and the learning parameter.

Selection of Training Patterns

The classification of total data (patterns) is classified into two groups they are training data, and testing data. The data which is used to train the network in order to find the relationship with respect to the input and output parameters.

Selection of Testing Patterns

Once the network training is done, the weights and biases are fixed and the network can then be run using same data. Inorder to test the network, it is needed to run the network with the training data in order to know whether the yieldsgood approximation to the known output.for these data,and then prepare the other for future scope which havenot been used while training the network. Then after the network should be run using this data to check the Correctness of this networktermed as generalization. It depends on the following parameters, size of the training data set, the architecture of the network, and thecomplexity of the problem. The Portion of testing data are taken at random, approximately (16%) from totaldatabase.

ANN

The successful application (speed of convergence and accuracy of prediction) of a neural network depends on selecting suitable configuration of the network. In order to define the configuration of the ANN; Method of trial and error was used. some aspects were fixed from beginning, including: 1node in output layer, and BPN algorithm. Nature of the problem is determined by the nodes in the input layer and output layer. To introduce the components of the input vector the parameters used are

1) % of added fibers(A), 2) w/c ratio as (W/C), 3) The mixing ratio (C:S: G), 4) The size of fiber (B) and 5) Time oftesting(T).

Normalizing I/O Data Set: -Before applying the input and output data sets to the neural networks normalization of the same is required to solve the problem of large numbers from replacing smaller numbers and also to overcome premature saturation of hidden nodes, which delays the training process.

Because of the large difference in the values of input and output values are restricted to a specific range.

The obtained output is in the form of an equation which has some Mean Square Error (MSE).

InitializationofWeights

Firstly, the initialization of weight factors between the nodes of different layers is to be done. Hence in this study two initialization functions are used: After each run the weight is and the ranges of random initialization function are [(-1to1), (-0.75to0.75), (-0.5to0.5) and (-0.25to0.25)].

Number of Nodes and Hidden Layers in Each Hidden Layer

1. The choice of the number of hidden layer and number of nodes in the hidden layer depends on the network application and selected based on the following rules:
2. forbothtrainingpatternsandtesting patterns.
3. The output network parameter should have an error which can be as small as possible

4. There should be fewer training epochs (number of iterations) as possible. In the present work, The network is tested in which one or two hidden layer configurations are used and the number of nodes in each hidden layer is increasing in order to test the network. The relationship between the target and output data shows that (R) Value is approximately equal toone.

Experimental Work, Output and Discussion

The results of the experimental work for 7 and 28 days age of concrete for the mixing ratios of (1:1.5:3) and (1:2:4) are observed. The results show that the highest value of the compressive strength is obtained with fiber adding 12% for mixing of (1:1.5:3) and 20% for (1:2:4) mixing. It may also be noted from this table that the optimum water cement ratio is 0.46 for mixing of (1:1.5:3) and 0.55 for (1:2:4) mixing.

Fig.1 Presents the results of the prediction of the compressive strength with various percentage of fiber addition for 28 days of concrete and (1:2:4) mixing proportion, using 1" nail size and w/c of 0.40. It can be observed that the compressive strength improves by about 89% with 28% increasing of fiber addition. Fig. 2. Shows the results of the prediction of the compressive strength with various percentage of fiber addition using 1" nail size for 28 days of concrete and (1:1.5:3) mixing proportion with w/c of 0.40.From these results, it may be concluded that the increasing of fiber addition up to 28% leads to increase the compressive strength of concrete about 81%.

Fig. 3. Presents the results of the prediction of the compressive strength with various percentage of fiber addition using 1.5" nail size for 28 days of concrete and (1:2:4) mixing proportion with w/c of 0.40.The above results showed that the increasing of 1.5” size fiber addition up to 28%, will increase the concrete compressive strength up to 21.5%. Fig.4. Presents the result of the prediction of the compressive strength with various percentage of fiber addition using 1.5"nail size for 28 days of concrete and (1:2:4) mixing proportion with w/c of 0.50. The results of the prediction of the compressive strength with various percentage of fiber addition using1.5" nail size for 7days of concrete and (1:2:4) mixing proportion with w/c of 0.40 were also determined.

It can be noted from above results that the compressive strength is increased by about 11.7% as the fiber addition increases 28%.

CONCLUSIONS

Few conclusions that can be obtained are below:

1. ANN has been proved to be efficient in predicting the compressive strength of FRC. The input parametersselected applying BPN algorithm, greatly influenced the training and generalization performance of network. In the process of training, the values of input patterns have a great impact on the training time as a result of theactivation function. Normalizing the input and target values of the training patterns seems to greatly reduce thetraining time.

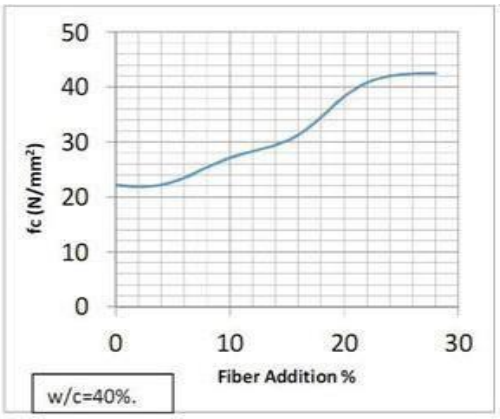

Fig.1 Compressive Strength vs. Fiber Addition Percentage using 1"nail size for 28 days of concrete and (1:2:4) mixing proportion.

The initial value of weight factors and biases has greatly influenced the efficiently (MSN) of the network model. Using both hidden layers, significantly improves performance of network. The factors like the training time, the mapping of the neural network are considered to determine the final number of nodes in each hidden layer and test patterns of the neural networks are monitored and generalized

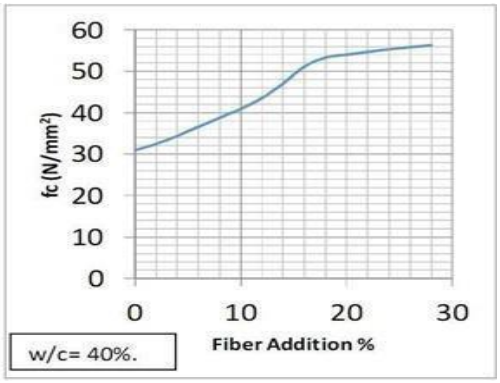

Fig.2 Compressive Strength vs. Fiber Addition Percentage using 1" nail size for 28 days of concrete and (1:1.5:3) mixing proportion.

It is found that the compressive strength is increasing more when the fibers added are 12% for mixing proportion 1:1.5:3, whereas for mixing proportion (1:2:4) the compressive strength is increased more when the fibers added are 20%. For mixing proportion (1:1.5:3) 46% of the optimum water cement ratio is found for 12%fibers in it. Whereas for mixing of (1:2:4) the ratio is found to be 55% with20% fibers.

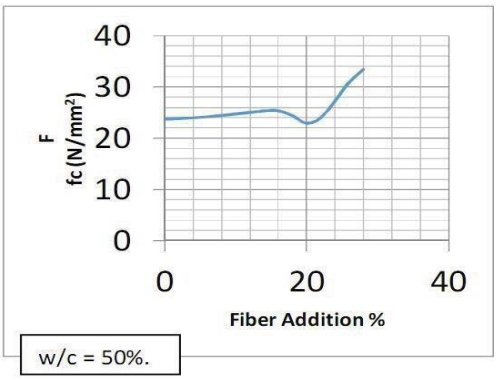

Fig.3. Compressive Strength vs. Fiber Addition Percentage using 1.5" nail size for 28 days of concrete and (1:2:4) mixing proportion.

By increasing the ratio of fibers using mixing proportion (1:1.5:3) the compressive strength is founded to be more uniform and effective upon the use of the mixing ratio (1:2:4). If there is less addition of larger size nails it is observed that there is an increase in the compressive strength but if the addition increases there is a decrease in compressive strength.

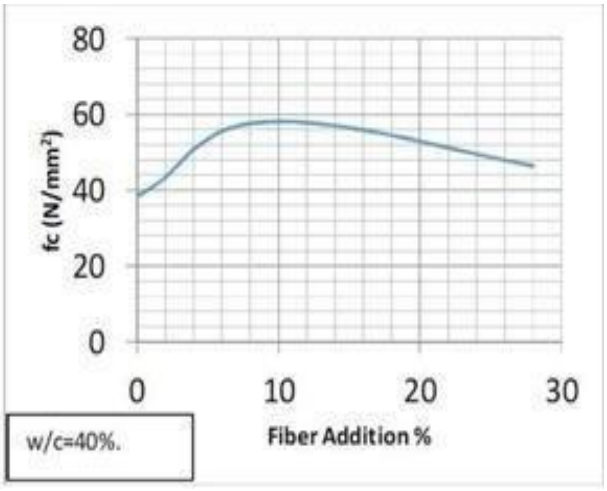

Fig.4 Compressive Strength vs. Fiber Addition Percentage using1.5" nail size for 28 days of concrete and (1:1.5:3) mixing proportion.

The uniformity and the effectiveness of the compressive strength is more, when the ratio of fibers added using mixing proportion (1:1.5:3) than using mixing ratio (1:2:4) when larger size of nails is added with low percentage, the compressive strength increases, whereas the increase in percentage of nails decreases the compressive strength.

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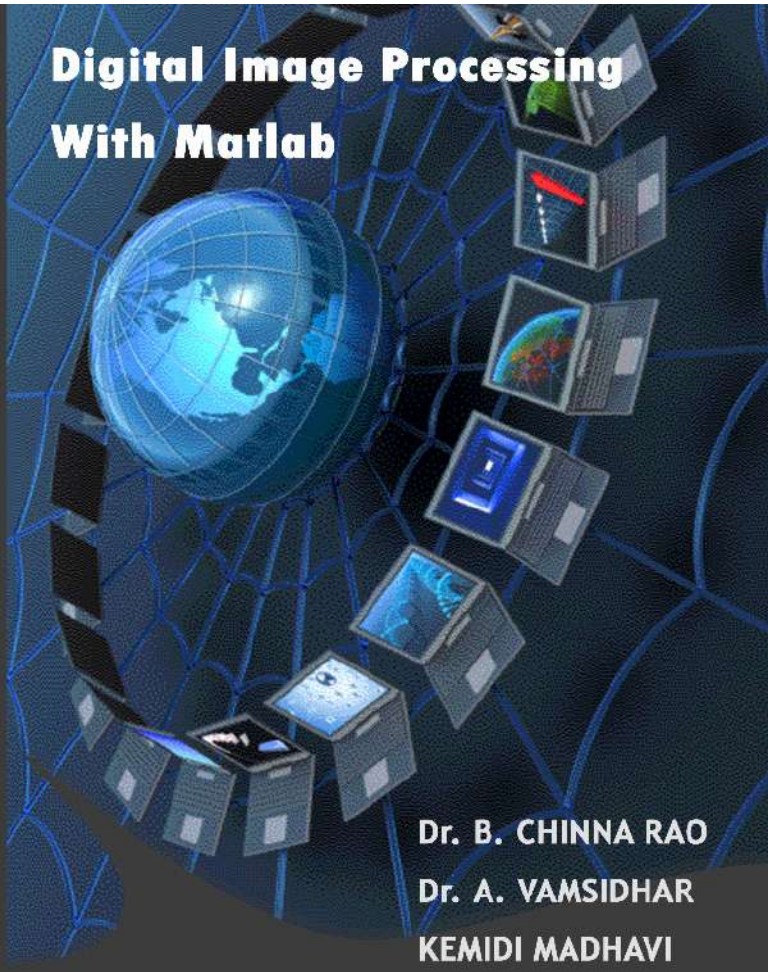

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Chapter

CNN Classification Approach to Detecting Abusive Content in Text Messages

By R. Dinesh Kumar, G. Vinoda Reddy, S. Ravi Chand, B. Karthika, V. Murugesh

Book Artificial Intelligence and Blockchain in Digital Forensics

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About The Book

Given the complexity of assessing and mitigating pollution—which may come from both natural and anthropogenic sources and in the form of, for example, biological, chemical, particle, or even energy—a multivariate strategy is needed. From the effects of pollution on human health to the need of establishing environmental fairness and finding long-term remedies, this book covers it all. This book aims to provide its readers with the knowledge they need to comprehend and apply cross-disciplinary strategies to environmental contamination issues of the present and the future.

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About Authors

Ms. Payal Arora is an academician holding experience of more than 15 years in teaching. She has done her M.Sc. in Environmental Science from Guru Jambheshwar University, Hisar in 1999 and Bachelor Degree in Education from Jammu University in 2000. She also holds Masters' Degree in Education. Ms. Arora's core areas of teaching are Biology, Environmental Science and Education management. At present she is working as a Science teacher for higher classes in Saraswati Academy (Affiliated to CBSE), Haldwani since 2012. A researcher, author, mentor and learner, she is eager to contribute in making a difference in society through her profession.

Dr. Rashmi Trivedi, Professor of Chemistry, NNRESGI, HYDERABAD. She did PhD in Chemistry from Devi Ahilya Vishva Vidalia, Indore (M.P.) in the year of 2000. She has 23 years of Teaching experience & published paper in reputated National & International journals. She delivered lecture in National level seminar as resource person & also act as an instrumental judge for national level oral & poster presentation compititions. She has one patent to her credit

Pavan Kumar Thimmaraju is an Associate Professor in Department of Mechanical Engineering at Nalla

Narasimha Reddy Education Society's Group of Institutions, Hyderabad. He did B.Tech.(Mechanical Engineering) from KLCE presently KL University, Andhra Pradesh. M.E (Mechanical Engineering with specialization in Tool Design)from Osmania University, Hyderabad, Masters certificate course in CAD/CAM/CAE from Central Institute of Plastics Engineering and Technology, Hyderabad, PGDIPR&CL from University of Hyderabad, LLB from Osmania University Hyderabad, LLM(corporate law) from Osmania University, Hyderabad ,PGDETM from University of Hyderabad, PGDSRD from NIRD, HYDERABAD. Submitted PhD thesis in Department of Mechanical Engineering, Osmania University, Hyderabad. Pavan Kumar Thimmaraju has an academic experience of 20 years and in the industry for three years before starting career in academic. He is involved in academic research and has published in papers in reputed journals and presented in national and international conferences. He has four patients to his credit.

Mrs. Pooja Maurya graduated in Electrical Engineering and obtained her master degree in Electric Drive and Control. She is presently working in Government Polytechnic Ghaziabad. Experience of more than 10 year.

Preface

Air and water pollution are among the most pressing global problems today. Many pollutants have a lengthy half-life in the environment and may damage people by inhalation, ingestion, skin absorption, and other pathways long after they have been released. Even while cutting-edge machinery doesn't release nearly as much waste as their antiquated predecessors did, we still need to set up safeguards to keep an eye on things and fix them if they start to go out of hand.

This work covers (i) pollution and environmental pollutants (ii) environmental impact and economic assistant, and (iii) Pollution control, measures and standards. The textbook aims to provide readers with the knowledge of pollutants and hazardous waste and treatments, long-term strategies they need to effectively manage, mitigate, and avoid environmental contamination.

The goal of this book is to show how physical in nature, chemical agent, and earth's surface, as well as biological sciences can be completely implemented with science and engineering, health and welfare, as well as social sciences, encouraging readers to employ multidisciplinary and interdisciplinary solutions to ancient times, present, as well as future environmental pollution problems.

Table of Content

Chapter 1

Environmental Pollutants

1.1. Understanding pollution and pollutants

1.1.1. Pollution

The evolution of toxins into the ecosystem's natural systems results in pollution, which has a negative impact. Every element such as solids, liquids, or gases can cause pollution. Both naturally occurring toxins and imported materials can be considered pollutants, which are the elements of pollution. Even though natural disasters can result in environmental contamination, the word pollution often suggests that the toxins came from an artificial source, or a source made possible by human activity. Point source and nonpoint source pollution are two common categories of pollution. Nine million individuals died worldwide in 2015 as a result of pollution. With little discernible improvement against pollution, this stayed unchanged in 2019. 34 of these previous deaths were caused by air pollution.

Noise pollution, land pollution, trash, air pollution, marine

pollution, industrial emissions, radioactive fallout, chemical pollution, light pollution, as well as water contamination are some of the most significant types of pollution.

Pollution is described as the existence of contaminants or polluted compounds in such concentration levels that, when contacted for a long enough period, have a deleterious effect on people, animals, plants, or productive resources. This lowers the life quality in the surroundings. The environment is negatively impacted by pollution on a large scale. When considered from the standpoint of the limits of the planet, human culture has unleashed unique organisms that are far beyond acceptable amounts.

1.1.2. Pollutants

A chemical or energy put further into the environment that seems to have unintended effects or negatively impacts a resource's usability is referred to as a pollutant or new entity. These may arise naturally such as minerals and any extracted chemicals like oil or may have human-caused origins. Among these include residential sewage, uneaten food, and pollutants that take several generations or more to leave the environment or that linger in the ecosystem for a very long time and are said to be slowly degrading or persistent. Examples include most polymers and the pesticide DDT.

By altering the growth rate of species of animals or plants or by affecting human conveniences, pleasure, wellness, or

property prices, pollution may inflict long- or short-term damages. Some contaminants are biodegradable, which means they won't linger in the environment for very long.

Pollution is the result of unfavorable changes in our environment that have a negative impact on humans, animals, as well as plants. Pollutants are any compounds that are produced by human activities that are present in greater quantities than they would naturally and have a specific impact on the environment.

The degree of a pollutant's harmful impact on human health depends on its concentration and type. The main pollutants are impurities that are discharged directly from the point of origin, such as Carbon (CO), Sulphur dioxide (SO_2), and Nitric Oxide (NO). When pollutants such as PAN (peroxy acetyl nitrates), petrochemical smog, and formaldehyde are created when pollutants like Hydrocarbons (HC), Nitric Oxide (NO), and Trioxide (O_3) mix in the environment.

Pollutants can be categorized as degradable, gradually degradable, or non-degradable from an ecological point of view. Degradable pollutants, also known as non-persistent pollutants, can be quickly decomposed by natural processes. For instance, domestic sewage, unfinished food, and Pollutants that slowly degrade or remain in the ecosystem are those that take several generations or longer to leave the environment and stay there for a very long time. Examples include the insecticide DDT and the

majority of polymers. Natural processes cannot decompose non-degradable contaminants. Nuclear wastes and poisonous components like mercury or lead are two examples of substances that are difficult to remove from the environment once they have been released.

1.2. Pollutants types

Pollutants are elements or materials that have an adverse effect on the environment and the species that inhabit it, degrading life. There are many different kinds of contaminants in the environment that harm the environment.

1.2.1. Types of Pollutants

Water Pollutants

Nowadays days, dangerous pollutants in water are responsible for the significant pollution that exists. It is mostly caused by overflow from industrial facilities, agricultural areas, and sometimes even urban areas. For example, hazardous pollutants found in industrial waste degrade water quality. Additionally, these contaminants promote the development of algae, which suffocates aquatic plants. In addition to that, it decreases oxygen levels, which are essential for the existence of organisms located underwater.

Raw sewage is also a significant water contaminant. It can result in many severe diseases and has a highly negative

effect on water quality. This occurs as a result of its occasionally dangerous mixing with drinking water supplies. In addition to that, there is waste that is improperly disposed of and ends ending up in the water. For instance, the accumulation of plastic bottles, packets, and other items in the water kills aquatic life.

Soil Pollutants

Additionally, the amount of contaminants in the soil makes it very difficult for the soil to maintain its fertility. Once more, industrial sources are a contributing factor. Furthermore, dangerous chemical waste is not properly disposed of, thus it ends up in the ground.

In addition, frequent soil contaminants include asbestos, PCBs, leads, excessive herbicide as well as pesticide use, and much more. As a result, it is imperative to handle these dangerous contaminants correctly.

Air Pollutants

Nowadays more than ever, the oxygen we consume is highly contaminated. The use of fossil fuels contributes significantly to air pollution. This occurs as a result of automotive use and manufacturing emissions.

Whenever fossil fuels are burned, smog and a dense coating of particulate matter that encloses sizable zones are created. Moreover, cancer, asthma, bronchitis, as well as other lung disorders are all respiratory issues that are greatly influenced by air pollution.

In addition, the air is contaminated with nitrogen oxides and sulphur oxides, which result in acidification. Both the forests' people and the forests themselves are badly impacted by these acid rains. Additionally, it deteriorates the quality of our structures, outdoor statuary, and memorials.

Light Pollutants

It is important to underline that light pollution can be quite harmful. It means that whenever there is a significant amount of light, it usually occurs in urban as well as heavily populated places. People are unable to observe the nighttime sky's features due to light pollution. Additionally, it impedes bird migratory patterns as well as the behaviors of animals that are active at night.

Noise Pollutants

Particularly in urban areas, noise pollution is increasing. In general, noise pollution is caused by people and their actions. These sounds are so loud that they impair life's functionality and quality. These include the horns on cars, speakers, fireworks, electrical equipment, and more. They restrict the mobility of marine mammals like dolphins and whales. They also have an impact on the success of bird nests.

1.3. Solubility of pollutants

A solution consists of a solvent and a solute which may be gaseous, liquids, or even solids. It is common for the

solvent to make up the bulk of a solution. It's the solute, rather than the solvent, that is causing the dissolution. The solubility of a substance is defined as the volume of solute required to generate a saturated solution in a certain amount of solvent at a fixed temperature. When plotting the solubility of material against its temperature dependence, it is easy to see that the solubility of most ionic compounds rises as the temperature rises. Also, the overall solubility of ionic substances at a given temperature is temperature-dependent because of solute-solvent interactions. Because of their intermolecular interaction, ionic substances can have an impact on solubility.

Solubility=grams of solute/100 grams of solvent

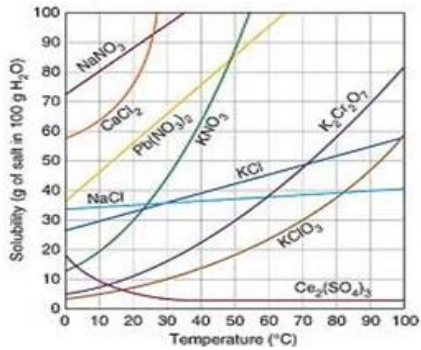

Figure 1.1: Solubility curve of ionic compounds.[*]

[*]https://chem.libretexts.org/@api/deki/files/82140/Gases.JPG?revision=1&size=bestfit&width=325&height=297https://chem.libretexts.org/@api/deki/files/82138/Solubility.JPG?revision=1&size=bestfit&width=317&height=314

Saturated solutions have the highest possible concentrations of solutes in a given volume of solvent at a particular temperature. When a solution is saturated, no more solute can be dissolved into the solvent and the system is in a dynamic equilibrium state. Saturated solutions can only dissolve so much solute, whereas unsaturated solutions can dissolve more. When a solution seems to have more solution than it can retain at a specific temperature, we say that it is supersaturated. A supersaturated solution is created by adding additional solute, heating the solution to boiling, and then letting it cool slowly without stirring. Sometimes crystallization requires the introduction of a seed crystal, and when this is done, the process may be fairly rapid and spectacular.

As temperature rises, so does the solubility of most liquid and solid solutions. But this is not the case with gases, whose soluble nature diminishes with rising temperatures. The reduction in solubility is caused by the molecules' constant motion. The kinetic energy average of a substance's molecules is what we call its temperature. Increasing the temperature increases the thermal energy because the molecules' kinetic energy increases. Because the molecules are moving around more quickly due to the increased kinetic energy, the intermolecular interaction is reduced, and the solute gas molecules are free to leave the solution. This is readily apparent when an opened can of soda is stored in a chilly refrigerator or at room temperature. A lot of the "fizz," or carbon dioxide, would have been lost during shipment, leaving the soda tasting

somewhat "flat" at room temperature. Because so much oxygen gas is lost during the boiling process, water that has been cooked also has a "flat" taste.

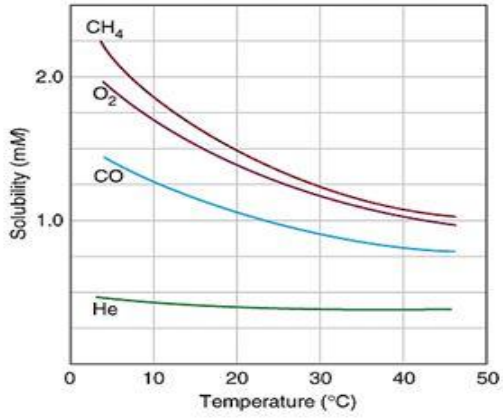

Figure 1.2: A graph of the solubility of gases versus temperature, showing that as the temperature of the solution increases the solubility of a gas decreases.*

Changing the temperatures of a stream, lake, or sea is an example of thermal pollution. This disrupts natural processes and affects aquatic ecosystems and the creatures that depend on them. Power generation plants as well as industrial enterprises that utilize fossil fuels and nuclear power are major contributors to thermal pollution because they discharge vast quantities of surplus thermal energy into the environment. The heat is transferred to the water, which boils into steam that drives turbines that produce power. Eventually, it will have to be discharged back into

*https://chem.libretexts.org/@api/deki/files/82140/Gases.JPG?revision=1&size=bestfit&width=325&height=297

rivers, lakes, or seas, and if it isn't cooled correctly, it might raise the temperatures of the surrounding water.

Deforestation and urbanization may alter the terrain around a body of water, leading to higher water temperatures. A ten-degree rise in water temperature is possible once trees are cut down around a body of water. When the terrain far away from the water body is changed, thermal pollution might still occur. Erosion, altered water volumes, and pollution are all possible outcomes of these landscape changes. An illustration of this is the fact that murky water is better at soaking up solar heat than pure water.

The temperature ranges of their immediate surroundings affect every aspect of an aquatic organism's life, from laying of the eggs to feeding activities to digestive and metabolism processes to reproduction to geographic dispersion to survival. To a large extent, ectoderms like fish rely on the absorption of gas in water for their own life. Since the solubility of gasses in water decreases with rising temperatures, boiling water contains less oxygen than cold water. As a result, many fish can only survive in colder waters where there is plenty of oxygen. Many aquatic creatures may only be able to survive in an environment that is just slightly beyond their metabolic range if thermal pollution becomes a concern. The oxidation of natural dietary materials is regulated by metabolic enzymes in many different types of organisms. Most metabolic enzymes have a preferred temperature at

which they catalyze at a rapid pace. Fish are very sensitive to even little temperature changes. In addition to reducing biodiversity, thermal pollution may create an environment that is susceptible to invasion by non-native aquatic organisms, which can have devastating effects on local ecosystems.

1.4. Transfer of pollutants within different mediums

Pollutants in the environment are shifted about due to three processes: transportation, dispersion, as well as deposition. Time-averaged air movement causes transfer. When the transfer is averaged over a while shorter than the duration of local disturbance, dispersion occurs. Pollutants in the air are carried to the ground via deposition processes such as rainfall, scavenging, and deposition.

Air pollution may then travel through the atmosphere, water, soil, live creatures, and food. The dispersion routes take many forms and are very context-dependent, both in terms of the emissions' origins and the pollutants' specific characteristics. Dissemination rates and patterns are also very context-dependent. Numerous variables impact the spread of air pollution:

- The weather,
- The height of the emission,
- The weather,

- The origination site

Pollutants undergo dynamic transformations and exchanges as they are dispersed. Because of dispersion in the air, concentrations are reduced. Pollutants are sorted into distinct piles or pools according to their individual physical properties. The initial contaminant is degraded or transformed into new chemicals through a series of chemical processes. Some pollutants may be eliminated from the transportation medium by deposition, such as by settling out because of the effects of gravitation, by rainwash, or by absorption by vegetation and other impediments.

Because of this, the dispersal patterns of many pollutants are exceedingly complicated, particularly in urban areas with their many different emission sources and wide range of weather conditions. Because of this complexity, it is sometimes difficult to estimate or assess pollutant trends and patterns making it hard to forecast human exposure levels.

Changes in pollution levels throughout time are crucial. The existence of long-term patterns often reflects fundamental shifts in emission rates. Beyond this, yearly fluctuations may be superimposed due to changes in the environment or source activity. As a result of activity cycles and short-term climate and other consequences, many pollutants also exhibit noticeable seasonal, weeklong, and everyday patterns. Large, transient

pollution outbreaks may also come from unexpected, inadvertent emissions.

Consequently, exposure data will change depending on the timing, location, and duration of air monitoring.

1.5. Concept of biotransformation and bioaccumulation

Both bioaccumulations, as well as biotransformation procedures, are crucial because they control the buildup of chemicals in food webs and establish the body's effective dosage. Toxic effects are caused by the internal dosage, also known as the physiologically relevant dose, which is the period of the substance's concentration within the body.

The liver plays a vital role in the metabolic process of biotransformation, which aids in the elimination of both foreign and endogenous chemicals. The chemical compositions of these molecules are modified via a sequence of processes. The substrates for these processes may be rendered inert, active, or even poisonous by the enzymes that initiate them.

1.5.1. Fundamentals of Biotransformation

There are three stages, or phases, to the biotransformation process. These responses might happen in rapid succession or rapid succession.

Phase I produces a molecule that is polar, water-soluble,

and often still functional. The products of this stage are often suitable substrates for the next stage.

- Cytochrome P450 oxidation
- Degradation
- Hydrolysis

Phase II produces water-soluble inactive molecules that are eliminated by the body, yielding a large polar metabolite by the addition of endogenous hydrophilic groups.

- Methylation
- Glucuronidation
- Acetylation
- Sulfation
- Glutathione conjugation
- Interaction of a peptide with an amino acid

Phase III: This happens after phase II, when a molecule may be metabolized and excreted in other ways. It belongs to the following subfamilies:

- The cassette that binds ATP (ABC)
- Carriers of solutes (SLCs)

Bioaccumulation refers to the slow build-up of compounds inside an organism, such as the accumulation of insecticides or other toxins. Bioaccumulation takes place when an organism takes in a material at a rate higher than its rate of loss or elimination via catabolism and excretion.

Therefore, even if atmospheric concentrations of the toxins are not particularly high, the danger of chronic poisoning increases if the living organism's half-life of the hazardous chemical is lengthy. Models may be used to foretell bioaccumulation, for instance in fish. There is no evidence to back up the hypothesis of a molecular size cutoff that may be used as an indication of bioaccumulation capacity. The bioaccumulation of substances in an organism may be drastically affected by biotransformation.

The bioaccumulation and biomagnification of metal toxicity are well-documented. Accumulation occurs when an organism stores or takes in metal at a quicker pace than it can metabolize and expel it. To better manage and reduce the negative effects of chemicals in the environment, it is important to have a firm grasp of the processes involved in bioaccumulation.

1.6. Concept of radioactivity

For reasons of nuclear instabilities, atomic nuclei may emit radioactive radiation. The unstable atom's nucleus loses energy by radiating it out into space. The nucleus is held together by the strong attractive forces of the nucleus and the electrostatic repulsion forces. Both of these factors are regarded as very potent in the wild. When the nucleus' mass is concentrated, it becomes quite large, which raises the probability of experiencing instability. This is why uranium and plutonium atoms are highly unstable, leading to the phenomena of radioactivity.

1.6.1. Laws of Radioactivity

- The breakdown of a nucleus produces radiation.
- The decomposition rate of the nucleus is unaffected by changes in either pressure or temperature.
- For radioactivity to occur, the conservation law of charges must be in effect.
- The offspring nucleus is distinct from the parent nucleus in terms of its chemical and physical features.
- Radioactive decay releases energy in the form of alpha, beta, and gamma rays.
- The amount of atoms in the sample at any one moment determines how quickly a radioactive chemical will decay.

1.7. Radioactive decay and half-life of pollutants

The particles of radioactive elements release nuclear energy in the shape of alpha, beta, and gamma particles via a process called radioactive decay. Simply calculating the amount of alpha, beta, and gamma radiation over a while is all that is needed to calculate radioactive decay.

The rule of radioactive decay was proposed in 1902. It proposes that the nuclei of radioactive elements spontaneously disintegrate into new elemental nuclei.

Radioactive elements, which may be found in the same section of the periodic table, are another word that can be

attributed to Soddy. The term "half-life" is used to describe the amount of time required for half of a radioactive material to decay.

1.7.1. Radioactive decay formula

The process of radioactive decay is a significant natural event that follows the rules of first-order chemical kinetics. Radiocarbon dating, often known as the age determination of matter or materials, is the primary application for its utilization. The equation for the frequency of radioactive decay only relies on one power of the radiation being measured.

Because of this, $dN/dt = kN$, where N represents the number of atoms of the radioactive element that is dissolving, dt is the amount of time during which the disintegration is recorded, and k is the constant for radioactive decay.

If there are N_0 atoms in the sample at the time $t = 0$ as well as N atoms in the sample after the time t, then the total number of atoms in the sample is N.

Radioactive decay constant:

According to the equation, $(dN/N)/dt = k$ = rate constant.

The proportion of the total number of atoms that breakdown in the given amount of time is denoted by the quantity dN/N. As a result, the radioactive decay constant is a representation of the percentage of radioactive atoms

that dissolve in one unit of time. The presence of a negative sign indicates that N is decreasing with time.

Half-life period:

After a given amount of time has passed, the value of (N0/N) will become equal to only fifty percent of the radioactive substances. The amount of time needed for radioactive material or compounds to decay by half is referred to as their half-life. Radioactive elements are distinguished by a certain feature known as their half-life.

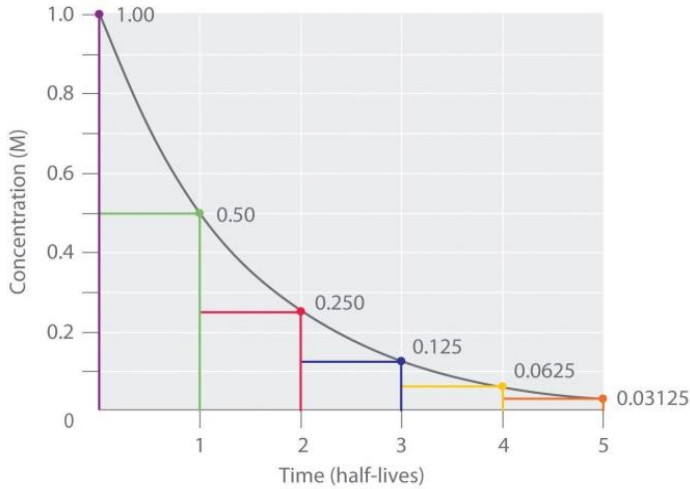

Figure 1.3: Radioactive Decay and Half-life*

Calculate the half-life:

The formula for radioactive decay:

* https://saylordotorg.github.io/text_general-chemistry-principles-patterns-and-applications-v1.0/section_18/261586c1c0844e5efa716d77033046ea.jpg

When time equals t12, and number equals N0/2, then:

$t½ = \ln 2/k = 0.693/k$.

The link between the half-life as well as the radioactive decay rates may be found in this equation. As a result, the half-life is not affected in any way by the quantity of the radioactive element that is present at any particular moment. The polonium-213 isotope has a half-life of 4.2 x 10-6 seconds, whereas the bismuth-209 isotope has a half-life of 3 x 107 years. Whereas if the radioactivity of the component is 100%, its half-life is 4 hours, then the element is said to be highly radioactive.

After 4 hours, it has decomposed to 50% as well as the remaining 50% has remained unchanged. After eight hours, it has decomposed 75%, and the remaining 25% has been used to continue the process. As a result, once n half-lives have passed, the quantity of the radioactive element that remains is (1/2)n.

1.8. Organometallic compounds

Organometallic compounds are a kind of chemical compound that has at least one bond between a metal element as well as a carbon atom that is part of an organic molecule. These compounds are known as organometallic compounds. Even metalloid elements like silicon, tin, as well as boron, are recognized as being capable of forming organometallic compounds, which are then used in a variety of chemical processes in the industrial sector.

Organometallic compounds may be used to facilitate the catalysis of processes in which polymers or medicines serve as the target molecules; in turn, it leads to an acceleration in the pace at which the reactions take place.

In most cases, the connection that exists between the atom of the metal and the carbon that is part of the organic complex is solid. The carbon that is bonded to the central metal atom in these compounds takes on a carbon ionic character when metals that have relatively high electro positivity are used in their formation. Examples of such metals are sodium as well as lithium.

The chemical seen above is an instance of an organometallic complex. In this particular compound, the carbon atoms that makeup benzene molecules link with chromium. Grignard reagents, tetra carbonyl nickel, as well as dimethyl magnesium are some examples of the sorts of chemicals that fall within this category.

1.8.1. Properties of Organometallic Compounds

The following are some of the characteristics of compounds that include organometallic elements stated in point form.

- In the environment, the link between both the metal as well as the carbon atom is very often characterized by a high degree of covalently.
- The vast majority of organometallic compounds may be found in solid forms. This is particularly

true for molecules in which the hydrocarbon groups are fragrant or possess a ring structure.

- Substances that are made up of highly electropositive ions like sodium or lithium are extremely volatile and have the potential to spontaneously combust on their own.
- It has been discovered that organometallic compounds are, in so many instances, harmful to human beings.
- The compounds that are generated by highly electropositive ions have the potential to function as reducing agents, and these compounds also have that potential.

As can be seen from the information presented above, the characteristics of organometallic compounds are not the same as those of other organometallic compounds since these characteristics are derived from the characteristics of the metals that make up these compounds.

1.8.2. Applications of Organometallic Compounds

The discipline of chemistry makes extensive use of organometallic compounds for a variety of different purposes. The following is a list of some of them:

- Homogeneous catalysts made from organometallic compounds are utilized in some types of commercially important chemical processes.
- These compounds are put to use as stoichiometric reagents in chemical processes that are conducted

for both commercial and academic purposes.

- The production of some semiconductors necessitates the utilization of substances including trimethylgallium, trimethylaluminum, trimethyl-indium, and trimethyl antimony. Certain compounds are used throughout the manufacturing process of these semiconductors.
- In addition to this, they are used in the manufacturing of light-emitting diodes (or LEDs).
- These chemicals are put to use in the bulk hydrogenation operations that take place during the manufacturing of margarine and other similar products.
- During the production of certain organic molecules, these compounds are put to use as catalysts and reagents, respectively.
- It is possible to facilitate the synthesis of a wide variety of organic molecules by making use of the complexes that are produced from organometallic compounds.

1.9. Acid mine drainage

The discharge of acidic water from mining sites or coal mines is referred to variously as mine drainage, acid and metalliferous drainage (AMD), or acid rock drainage (ARD).

Acid rock drainage is a natural occurrence in some environments as a result of the rock weathering of rocks,

but it is aggravated by the large-scale earth disruptions that are defining features of extraction as well as other major construction activities, typically in rocks that contain an abundant supply of sulfide minerals. This occurs most commonly in rocks that are volcanic in origin.

The formation of acid rock drainage is possible in locations such as building sites, subdivisions, and traffic corridors where the earth's surface has been disrupted. It is possible for the liquid that descends from coal stockpiles, coal handling equipment, coal washeries, as well as coal waste tips to be very acidic, and when this occurs, the liquid is referred to as acid rock drainage. This occurs in many different areas. This liquid often carries noxious metals like copper or iron in its composition. These, in conjunction with the decrease in pH, produce an effect that is damaging to the aquatic habitats of the streams.

The same kinds of chemical processes and reactions can take place when acid sulfate soils that were developed in coastal or estuary conditions after the most recent significant increase in sea level are disturbed, and this creates a threat to the ecosystem in the same manner.

Acid Mine Drainage

- Mines constructed as earlier as the 1800s were designed in a way that made use of gravity drainage. This was done to prevent an excessive buildup of water inside the mines.
- As a direct consequence of this, water that was

contaminated with acid, iron, sulphur, and aluminum washed out of the mines and entered the rivers.

1.9.1. Results of Acid Mine Drainage:

- Another of the most significant causes of water contamination in Region 3 is called acid mine drainage.
- The governments are concerned about it not simply from an ecological standpoint but also an economic one.

1.9.2. Economic Concerns Resulting from Acid Mine Drainage:

A region that is influenced by acid mine drainage often experiences a decline in valuable recreational species of fish such as trout, along with a continuous decrease in outdoor tourism and recreation in addition to groundwater pollution of groundwater drinking supplies. This is in addition to the fact that acid mine drainage can cause a region to lose valuable recreational fish species.

1.10. Causes of soil pollution and degradation

The term "soil pollution" refers to the process through which the earth's surface becomes tainted with a variety of pollutants, including hazardous substances derived from goods created by humans as well as natural pollutants such as wind and precipitation. The chemicals that are already present in the soil will react with any new

chemicals that are added to it, which may result in the contamination or pollution of the soil.

If the substance that is put into the ground is inorganic and hazardous, then perhaps the soil would become contaminated or polluted, which may result in a great deal of potential damage to the ecosystem. On the contrary, side, even if the pollutant is a natural element of the ground, it may still create soil contamination if the level is already high. This is because natural components of the soil tend to have lower concentrations than man-made contaminants.

1.10.1. Main Causes of Soil Pollution

The phenomenon known as soil contamination is rather complicated and its onset may be caused by a wide range of items and actions, including the careless disposal of cigarette butts and an excessive application of chemical fertilizers. Every effect is connected to some other cause. It is pretty tough to identify one single reason. On the other hand, the most important factors are detailed below.

1. Industrial Activity

The most significant contribution to the issue for the last century has been industrial activity, particularly given the rise in the quantity of manufacturing and mining that has taken place. The mining of minerals from the soil is essential to the majority of different sectors.

Whether it's iron ore or coals, the by-products are polluted,

and they aren't dumped off in a way that can be deemed to be safe. Because of this, the waste from industrial processes stays on the surface of the soil for a significant amount of time, rendering it unfit for any use.

2. Agricultural Activities

Since technological advancements have given us access to sophisticated insecticides and fertilizers, there has been a significant increase in the number of chemicals that are being used. They are loaded with elements that are not found in the environment and therefore cannot be decomposed by nature since they are not naturally occurring.

As a consequence of this, when they have combined with water, they permeate the earth and gradually diminish the soil's fertility. Certain chemicals cause harm to the structure of the soil, making it more susceptible to erosion from both water and air. Several of these pesticides are absorbed by plants, and as the plants die and decay, they contribute to the contamination of the soil since chemicals get to be a part of the ground.

3. Waste Disposal

Lastly, how people discard away garbage is becoming an increasingly significant source of concern. In addition to the pollution that is almost certainly caused by industrial waste, there is still another way in which humans contribute to the problem. There is a specific quantity of

bodily waste, in the form of both urine and feces that is produced by each individual.

Although a significant portion of it is disposed of through sewage systems, there is also a significant quantity that is discarded directly into dumpsters in the form of disposables. Even the sewage system is terminated at the landfill, which is a source of water and soil pollution due to the disposal of biological waste. This is because our bodies contain a wide variety of poisons and chemicals, which are now leaking into the ground and contributing to the contamination of the environment.

4. Accidental Oil Spills

When chemicals are being stored or transported, there is always the risk of oil spills. This is something that can be observed at the majority of gas stations. The fuel contains compounds that degrade the soil's quality and render it unfit for agricultural use, thus using it to grow crops is not an option. These pollutants can find their way through the surface and into the underground, rendering the water unfit for human consumption.

5. Acid Rain

Pollutants that are already present in the atmosphere may contribute to the formation of acid rain by combining with raindrops and then falling to the ground. The composition of the soil may be altered as a result of the contaminated

water's capacity to dissolve away a number of the vital nutrients that are contained in the soil.

1.10.2. Soil degradation

The term "soil degradation" refers to the deterioration of soil quality that occurs as a result of incorrect use of the land or inadequate management of it, often for agricultural, industry, or urban reasons. It is a severe environmental concern. The earth's soils are not only an essential natural resource but also the bedrock upon which all life on land is built. Protecting the quality of the soil should be a top priority for preserving our health.

Examples of soil degradation

Degradation of soil occurs when the chemical, biological, and physiological aspects of soil quality deteriorate. Lack of organic material, deterioration in soil quality and construction quality, erosion, unfavorable shifts in salinity, acidity, or acidity, and the impacts of toxic substances, pollutants, or severe floods are all potential causes. Soil deterioration may involve:

- Gully erosion, sheet erosion, as well as rill erosion are all types of water erosion.
- Wind wear and tear
- The term "salt content" refers to dry terrain, irrigation, and urban areas as well.
- A depletion of organic material
- Fertility decrease

- Either the acidity or acidity of the soil
- Among the causes of building, deterioration is soil compression and surface sealing.
- Large-scale movement
- Pollution of the soil, including the impacts of hazardous chemicals and other contaminants

1.11. Effect of soil pollution on the environment

Water pollution can occur when dangerous substances seep into groundwater or when polluted discharge or wastewater, which could also contain toxic heavy metals, reaches rivers, ponds, or seas from polluted soil. Air pollution is aggravated by the more toxic substances of the various soil types, as their release into the atmosphere is proportional to the amount of air pollution they cause. Heavy metals may build in the soil to the degree where they kill plant life if they are used too often or in excessive quantities.

Also, the breakdown of organic matter in polluted soil may produce sulfur dioxide as well as other sulfur compounds, contributing to acid rain. Moreover, microorganisms that help the soil quality by decomposing organic matter and facilitating water flow are harmed by the acidic environment produced by acidic soils caused by the accumulation of acidic substances like sulfur dioxide carried by the combustion of fossil fuels. Polluted soil may change plant metabolism, lowering crop yields and perhaps poisoning plants and trees that eat them. Acid

rain's pollution of soils affects plants because it alters soil chemistry, limiting the plants' capacity to take up nutrition and engage in photosynthesis.

Damage to the soil and the natural nutrients it contains reduces plant growth, which in turn leads to soil erosion and throws off the delicate balance of life there. While aluminum may be found in the environment naturally, soil pollution can cause inorganic forms to get mobilized; these are very harmful to plants and can seep into the ground water, where they can have a multiplied impact. As a result of pollution, the saltiness of the soil rises, rendering it unsuited for plant growth and rendering the land unproductive and barren. There is a risk that any plants that do manage to flourish here will be so toxic that eating them would be detrimental to human health.

Soil contamination may also lead to the production of poisonous dust. Further, nitrogen and phosphorus-rich polluted soils may leak into rivers, leading to algal blooms that, in turn, kill aquatic plants owing to a lack of dissolved oxygen. Finally, plant death may be attributed to salinization into the soil, which reduces the soil's capacity to buffer variations in the soil pH.

1.12. Control strategies for Soil Pollution

Soil is essential to the natural surroundings. While air and water pollution have received more attention, soil pollution management and prevention are just as critical. Because it provides a home to a diverse array of creatures

and plays a more significant part in the dispersal of plant species, the soil may affect water and air quality.

The soil also serves as a reservoir and a sink for gas emissions. As a result, it affects the movement of water and chemicals between both the ground and the air. Soil quality has declined over time due to human activities including pesticide, fungicide, and herbicide usage. Soil contamination is caused by a variety of human activities, not only farming.

Some strategies for limiting soil contamination are listed below:

1. Get a better understanding of the soil environment quality baseline

Sensitizations and studies on soil pollution may help all parties understand where they are in terms of the quality of the soil environment, which is essential for the effective management and prevention of soil erosion. However, the technical criteria for the survey, including the frequency at which the survey should be done, should be specified to guarantee consistent findings.

The frequency with which soil is monitored may also be increased by establishing networks to do so. To provide more extensive and dynamic data updating, it is also important to improve the administration of soil environmental information. Assuring prompt answers when they are needed requires both more data sharing and

a consistent sharing pattern.

2. Develop necessary legislation on soil pollution control

Soil pollution management initiatives are underway, but they might be sped up with the help of new laws. We need to review and update the current registers, such as those for urban and rural development, farming techniques, and land management, to reflect the most up-to-date methods for preventing and controlling soil contamination.

It is also important to revise laws governing the use of pesticides, the clean-up of polluted areas, and the care of soil on farms. Additionally, steps should be taken to encourage the perennial enhancement of soil pollution management requirements.

3. Proper management of agricultural land and the practice of organic farming

The prevention and management of soil contamination are greatly hampered by inefficient land use. Loss of organic compounds, topsoil, nutrients, and the soil's capacity to hold water are all symptoms of agricultural land pollution, which is a leading cause of soil fertility deterioration. Conservation of agricultural soils is best accomplished via a combination of mechanical and biological ways of management.

Agriculture and forestry both benefit from biological approaches to soil management. Crop rotation, crop management, contour planting, protector belt, crop wastes,

and the use of organic manure are all examples of crop-related management techniques.

Soil erosion is another major problem that forests help resolve. Creating new forest cover in arid regions helps maintain soil fertility and prevents soil formation from being washed away by rain and wind. It is important to reforest regions that have suffered from severe pollution or surface deterioration. Bunds, gully management, and contour holding systems are all examples of mechanical approaches to reducing soil pollution. Bunds built across slopes are an effective erosion control measure in locations with steep gradients.

4. Proper Solid Waste Treatment

There should be a treatment process in place before solid waste is released into the natural environment. Contamination of soils from wastes with high acidity or alkalinity may be prevented by neutralizing them beforehand. Its best practice to compost organic waste in a contained area before releasing it outside. The effective management of sewage sludge is a prime example of this.

The level of contamination should also be used to classify the trash. Mildly or moderately polluted materials may be treated in contained settings before being released back into the wild, whereas highly contaminated materials need intensive management, treatment, and control.

5. Ensure proper investigation of reclaimed land

Soil analysis and assessment are necessary when working with land that will be recovered and used for other reasons, such as the building of residential dwellings or social facilities like schools, such as the situation in the mining industry. The responsible municipality or government agency should be assigned the responsibility of conducting pollution tests in these areas.

Depending on the intended use of the land, the test findings will inform management and control strategies. If testing reveals the reclaimed ground to be contaminated, all planned activities there must be halted and the responsible entity must take measures to not only control and minimize the risks but also to avoid the pollution of nearby soils.

6. Strictly control the pollution of new soil

Preventing soil pollution is preferable to managing contaminated soil since it saves money. This means that safeguarding unpolluted soil should be the primary goal. To make sure a piece of land is fit for its intended use, it is important to do some digging before breaking ground. Furthermore, strict measures should be implemented against people who unlawfully discharge pollutants or who dump dangerous or toxic chemicals into the mudflat, sands, floodplains, or salt marshes.

The monitoring of unused spaces is also crucial. Environmental and soil capacities should inform improved government spatial planning and management. Non-ferrous metal metallurgical and cookery industry growth near residential areas and undeveloped land should be restricted.

Chapter 2

Water Pollution

2.1. Measurement of Water Quality

Water quality is measured by using a variety of tools, including Secchi disks (which test water purity), hooks, fishing gear, sensors, and gauges, by scientists. Direct sampling isn't the only method used to evaluate water quality. Aerial and satellite photos, together with careful observation of the natural atmosphere and the collection of creatures native to the body of water, may provide useful information.

Simple tests may give you an indication of the purity of a body of water, even if you do not have enough access to the tools that a scientist would:

Temperature

Water's temperature may have far-reaching effects. Although certain creatures thrive in cold water, others thrive in warm water. In general, aquatic species lack a warm-blooded metabolic system. This indicates that their internal body temperatures are consistent with those of

their environments. The temperature may affect processes occurring inside their bodies, such as photosynthesis and digestion. Water may store more dissolved solids (such as salt or sugar) at higher temperatures, but less dissolved gases like oxygen. Hot water promotes bacterial growth in general. There is more oxygen in cold water, making it ideal for fish as well as insect larvae.

Dissolved Oxygen (DO)

Many marine creatures can't make it without a steady supply of oxygen. The amount of oxygen available to fish and other aquatic species may be determined using this test. High amounts of dissolved oxygen (DO) are typical of healthy aquatic environments. Natural low dissolved oxygen (DO) levels occur in certain areas of water, such as marshes. A reduction in DO content may result from an influx of organic detritus. All the oxygen present in the water is used up by the microorganisms digesting the organic matter. Plant photosynthesis and air currents over the water's surface both contribute significantly to the oxygen content of the water.

pH (acidity)

The capability of hydrogen, or pH, is a measurement of acidity, with values ranging from 0 (very acidic) - 14 (highly basic), with 7 being a balanced pH level. The typical range for water's pH is between 6.5 and 8.5. Let's look at some real-world pH-value comparisons. Juice from a lemon is acidic due to its pH level of 3. The pain of

getting lime juice on a wounded finger is something everyone can relate to. If an acid spills, it may chew through almost any material. With a pH of 11, liquid bleach is a strong base. The skin may be burned by strong bases just as easily as by acids. The majority of our cells and tissues are water. The pH of water is 7. Things having a pH near 7 are generally safe for human consumption. It's the same with marine life. They are vulnerable to the effects of either an acidic or basic water environment. Some bases and acids are useful and even beneficial. Tomatoes, as well as aspirin, are both acids, whereas milk of magnesia & baking soda would both base.

Turbidity

The clearness of water is measured by a term called turbidity. How much and how far down into the water the light travels is determined by this. In excess, turbidity may be caused by soil erosion, dissolved sediments, or microbial development. Light may be blocked by any of these. Plants cannot survive in the dark. Reduced plant life means less oxygen in the water. The decaying vegetation also contributes to the organic detritus that microbes may feast on. There will be even less oxygen in the water as a result of this. When there isn't enough oxygen in the ocean, marine life dies.

2.2. Water Supply

The term "water supply" refers to the conveyance of water, whether by governmental utilities, commercial

organizations, community projects, or even individual efforts, often via a network of pumps and pipes. For society to thrive, public water delivery systems are required. The world's population relies on these networks to provide them with potable water. Consistency of supply, water quality, and adequate water pressure are all components of service quality. Institutional responsibilities for water distribution are structured differently between areas and nations. Problems with regulatory frameworks, service delivery, and uniformity are common examples.

To a far less degree than the fixed costs, the quantity of water used mostly affects the variable energy costs and chemical products that go into delivering the water. Almost everywhere in the globe, service providers must levy tariffs on customers to recoup some of their expenses.

Irrigation, the technique, and technologies of supplying water on a bigger scale, for a broader range of applications, principally agricultural, is a different issue from the water supply.

Depending on the system's needs, water may be sourced from groundwater, surface water, or even the ocean through desalination. Common water treatment procedures include filtration, chlorination, and sometimes fluoride to eliminate waterborne pathogens. For signs relating to the efficacy of drinking water distribution, see non-revenue water. After treatment, water is either gravity-fed or pumped to reservoirs, which may be high

like water towers or on the ground. After being put to use, water often goes through a sewage treatment facility before being released into a waterway like a stream, lake, or ocean.

2.3. Water Treatment

To make water suitable for a certain use, it must undergo a variety of processes. Many other things may be done with the water after it's been purified, including drinking, supplying industries with water, irrigating crops, maintaining river flows, providing for recreational purposes, and returning it to the environment. Purifying water for its intended use involves removing or diluting impurities and unwelcome components. Having access to clean water for both irrigation and drinking is essential to human health, which is why this process is so important.

Water is the most important substance on Earth, and access to clean drinking water is a major issue all around the globe in the twenty-first century. Pure water is an essential prerequisite for all forms of life. Even while water makes up more than 71% of the Earth's surface, only about 1% is drinkable under international standards owing to numerous contaminations. The main causes of water pollution include industrial waste water discharge, agricultural contamination, municipal sewage, and ecological and global changes. Metals, pigments, and microorganisms are harmful to humans, aquatic ecosystems, and the environment even at minute

concentrations. There are now 2.3 billion people in water-stressed nations, including 733 million people in high and severely water-stressed countries, as reported in a study.

Recovering water from existing wastewater or creating new sources of water for human use is necessary to deal with water shortage problems.

There are two main categories of wastewater: household and industrial. Wastewater, virus, microorganisms, non-toxic and toxic organisms, sanitary waste, garbage, detergent, and other liquid and solid emissions from non-industrial activities are all components of domestic wastewater.

2.3.1. Water treatment steps

Water purification processes often used by public water systems include coagulating flocculation, sediment, filtration, as well as disinfecting.

Coagulation

The initial stage of water purification often involves coagulation. To achieve coagulation, a positive-charged chemical is often included in the water. Dissolved dirt and other particles with a negative charge are rendered non-reactive by the positive charge. This leads to the particles combining with the substances to generate particles that are marginally bigger than before. In this stage, common substances include various salts, aluminum, and iron.

Flocculation

Next comes the flocculation stage, which follows coagulation. Gentle stirring of the water, known as flocculation, results in bigger, heavy particles called flocs. During this process, water treatment facilities often introduce extra chemicals to aid in the formation of flocculation.

Sedimentation

Sedimentation is a common process used in water treatment facilities to remove suspended materials. Because they are denser than water, flocs sink to the bottom of the body of water during the sedimentation process.

Filtration

After the flocs have sunk to the bottom, the purified water at the top of the tank may be filtered to remove any remaining particles. The process of filtering involves sending the clean water through a series of filters consisting of sand, gravel, and charcoal, all of which have pores of varying sizes. Dirt, chemical, bugs, germs, and viruses are all eliminated along with other dissolved particles by these filters. Bad scents are also eliminated by activated carbon filters.

Ultrafiltration is a technique that may be used in water treatment facilities in combination with or instead of conventional filtration. Ultrafiltration involves passing the

water via a filtration membrane with very tiny holes. Water as well as other small molecules, such as salts and small organic particles, can pass through this filter.

Disinfection

Any leftover parasites, microorganisms, or viruses in the water are eliminated by adding a chemical disinfectant at the water treatment facility, which might be chlorine, chlorination, or chlorine dioxide. Water treatment facilities will ensure minimal quantities of chemical disinfection are present in the water before it is released to the public. The leftover disinfectant is effective against microorganisms that make their home in the water distribution system between the treatment facility and your home.

2.4. Collection of Wastewater

Systems for collecting and transporting wastewater from residences, commercial establishments, and industrial facilities are planned and constructed. Dissolved materials and suspended solids in water are major sources of pollution. The collecting system should be built and configured such that wastewater moves at a rate of around 2.5 feet a second. Overly high or under-driving velocities might cause problems for the collecting system. To remove contaminants before discharging them to a body of water, the wastewater collecting system transports the sewage and particles to a treatment facility.

Most wastewater transport systems make use of the incline

of the terrain to move wastewater using gravity. This is why facilities dedicated to improving water quality tend to be situated in low areas close to the bodies of water they serve. Sanitation lifts or pumping stations are necessary to move sewage from a low location to a higher position so that gravity may be used to transport the wastewater for the rest of the period to the treatment center. In places with steep or rolling terrain, wastewater transportation to the water treatment facility may need many lift stations. Additionally, the farther the wastewater must be delivered to the treatment plant, the more likely it is that multiple lift stations will be necessary.

Used water from homes and businesses is collected through a network of gravity pipelines, manhole covers, containers, lift systems, security mechanisms, and force mains before being sent to a treatment facility. This effluent must be collected through a network of hundreds of miles of pipelines before it can be cleaned and released back into the environment.

2.4.1. Components of waste water collection system:

Several functional parts of the collecting system are shown and described in the following sections:

House Sewer: The house sewage is responsible for transporting wastewater though a building to the mainline or branch lines.

Lateral & Branch Sewers: Lateral and branch sewage are

what you'll find in the higher reaches of a municipal sewage system. When a lateral sewer line reaches its upstream end, it connects to a branch sewer, which then carries the effluent from all the other lateral sewer lines downstream.

Sub-main Sewers: Sub-main Sewer systems are the endpoints of several lateral and branch sewage that serve a larger region, neighborhood, or apartment building. Garbage is moved to a larger trunk sewage line, lifting station, or municipal packaged groundwater resources treatment facility.

Trunk/Main Sewers: A system's trunk/main sewers are its most important arteries for transporting wastewater to treatment plants. Wastewater is collected from several major sewage lines and sent to a treatment plant for water or interceptor sewers.

Interceptor Sewers: To go to a wastewater treatment plant, effluent from trunk sewers is intercepted by interceptor sewers. These pipes are the longest and widest in the sewage system, and they drain into the ocean.

Lift or Pump Stations: Platforms are used to raise (pump) wastewater to a higher altitude when the path traveled by gravitational sewage would need the sewage to be located at an inadequate incline or an unacceptable depth. The wastewater volume to be processed and the level to which it needs to be lifted determine the size and kind of lift station required.

2.5. Wastewater Treatment

Wastewater treatment is often used as a synonym for sewage treatment. To recycle wastewater back into the water cycle, it must first be treated to eliminate any impurities. Water reclamation occurs when wastewater is returned to the hydrological cycle or reused in a way that does not negatively affect the environment. A wastewater treatment facility is the location of the treatment process. It's important to get your wastewater to the right sort of treatment facility since there are various types. Domestic wastewater treatment facilities, also known as municipal wastewater treatment facilities, or simply sewage treatment facilities, are designated for the processing of municipal wastewater. Treatment of industrial wastewater occurs either in a dedicated industrial sewage treatment plant or, after preliminary treatment, at a sewage treatment facility. Agricultural sewage treatment plants and landfill treatment plants are two further kinds of facilities that treat wastewater.

Phase separation methods like sedimentation, as well as biological and chemical methods like oxidation and polishing, are often used in wastewater treatment. Sludge is the primary waste product of wastewater treatment facilities and is often processed further at the same or another facility. If anaerobic treatment methods are used, biogas is a potential secondary product. Reclaimed water is wastewater that has been purified and reused. Sewage treatment is performed so that it may be safely disposed of

or reused. However, the proper treatment technique can only be applied to the wastewater if the disposal and reuse alternatives are taken into account first.

2.5.1. Types of treatment plants

Different kinds of wastewater need different kinds of treatment in wastewater treatment facilities. Depending on the kind and degree of pollution, a wide variety of methods exist for treating wastewater. Physical methods, chemical processes, and biological systems all contribute to the therapy.

Wastewater treatment facilities may be classified as one of the following:

1. Sewage treatment plants
2. Industrial wastewater treatment plants
3. Agricultural wastewater treatment plants
4. Leachate treatment plants

Sewage treatment plants

Sewage treatment, also known as domestic wastewater treatment or municipal wastewater treatment is a form of wastewater treatment that seeks to eliminate water pollution caused by sewage discharges by removing contaminants from sewage and producing an effluent that can be safely released into the environment or reused. Sewage is a mixture of domestic and commercial wastewater as well as pre-treated industrial wastewater. Many different methods exist for cleaning wastewater. The

term "sewerage" refers to the network of pipelines and pump stations used to transport wastewater to a treatment plant, and it may be used to describe anything from small, locally managed systems like on-site treatment facilities to massive, centralized systems. Cities that use a combined sewer system funnel both sewage and urban runoff (storm water) into a single system. The primary and secondary treatments are the two basic phases of sewage treatment, with tertiary treatment including polishing procedures and nutrient removal in more modern systems. Both aerobic and anaerobic biological processes are used in secondary treatment to lower the amount of organic matter in sewage, which is expressed as the biological oxygen demand.

There are a variety of sewage treatment methods available today, the vast majority of which use biological processes. When deciding on appropriate technology, engineers and other decision-makers must weigh not just the quantitative and qualitative features of each option, but also the technological and economic factors at play in each. The quality of the effluent, the price of construction and operation, the cost of land, the amount of energy needed, and the environmental impact of the project are all important considerations. Sewage is often handled by different on-site sanitation methods rather than carried through sewers in low-population urban and rural regions of the world. Many different kinds of systems fall into this category, such as septic tanks with drainage fields, on-site sewer systems (OSS), and vermifilters.

Some estimate that only around 52% of wastewater is treated on a worldwide scale. Nevertheless, there is a significant disparity in how fast various nations handle their sewage. For instance, whereas developed nations handle an average of 74% of their wastewater, low-income nations treat just 4.2%.

Industrial wastewater treatment plants

The term "industrial wastewater treatment" refers to the methods utilized to clean up the wastewater that businesses generate. Treated effluent from industry may be recycled or discharged into a sewage system or water body. Wastewater from some factories may be processed at wastewater treatment facilities. Oil refineries, chemical industries, and petrochemical facilities all have specialized wastewater treatment facilities on-site to ensure that their wastewaters meet federal and state laws before being discharged into sewers, waterways, or the ocean.

Industries that produce wastewater with high quantities of organic materials such as oil and grease, hazardous pollutants such as heavy metals, volatile organic compounds (VOCs), or nutrients such as ammonia are included. Industries that generate wastewater may construct a pre-treatment system that removes certain pollutants, such as hazardous chemicals, before discharging the partly treated effluent into the municipal sewage system.

Almost all commercial operations result in the discharge of

wastewater. Recent tendencies have been toward either cutting down on output or finding ways to reuse treated wastewater already created by the factory. Some sectors have succeeded in revamping their production processes to minimize or eliminate pollution. Water from industries such as those that produce batteries, chemicals, electricity, food, steel, and iron metalworking, mineral mining and quarries, nuclear power, petroleum refineries, petrochemical products, pharmaceuticals, paper and pulp industrial facilities, textile factories, industrial oil pollutants, water purification, and wood preservatives all contribute to the problem of industrial wastewater. Saltwater treatment, solids removal through methods like chemical precipitation and filtering, oils and grease removal, biodegradable organics removal, other organics removal, acids and alkalis separation, and hazardous substance removal are all examples of treatment procedures.

Agricultural wastewater treatment plants

Controlling contamination from confined animal activities and from runoff water that may be polluted by chemicals in fertilizers, pesticides, animal slurry, crop residues, or irrigation water is an important part of farm management, and here is where agricultural wastewater treatment comes in. Treatment of agricultural sewage is essential for ongoing confined livestock activities like dairy production. Mechanical treatment units, such as those used in industrial wastewater, may be utilized in plants to do this

task. Ponds, settling basins, and facultative lagoons, if the land is available, may offer reduced operating expenses during breeding and harvest cycles. Typically, animal slurries are stored in anaerobic lagoons for treatment before being disposed of by sprinkle or trickling application to grasslands. Sometimes man-made wetlands are utilized to help in the processing of animal feces.

Sediment runoff, nutrient runoff, and pesticides are all examples of pollution from nonpoint sources. Animal waste, silage liquor, milk parlor (dairy farming) waste, slaughterhouse waste, vegetable washing water, and firewater are all examples of point source pollution. Due to surface runoff, many farms contribute to nonpoint source pollution that is not managed by a treatment facility.

Leachate treatment plants

Landfill leachate is often treated at specialized facilities called leachate treatment plants. Various electrochemical treatments, such as electrocoagulation, are also available. Reverse osmosis membrane filtering with disc tube module technology is another viable alternative.

2.5.2. Unit processes

Physical processes like settling or sedimentation, and biological processes like oxidizing or anaerobic treatment are examples of the unit processes used in wastewater treatment. There are several kinds of wastewater, and each one has its unique treatment strategy. Sedimentation is the

most common and basic method for separating particles from liquids in wastewater treatment. An effluent stream with increasing purity is created by gradually converting dissolved particles into solids, often a biological floc and biofilm, which would be subsequently settled out or segregated.

1) Phase separation

Through the process of phase separation, contaminants are removed to a non-aqueous medium. To get rid of the solids produced during oxidation or polishing, phase separation may happen in the middle of a treatment process. Reusing grease and oil as a fuel source or in soap production is possible. Sludge at a sewage treatment plant typically has to be dewatered because of the presence of solids. Options for disposing of dried solids depend on the kind and quantity of contaminants eliminated from the water.

- **Sedimentation**

Whenever density differences are great enough to overcome scattering through turbulence, solids like stone, grits, and dirt may be extracted from wastewater using gravity. The grit is settled out and the less dense particles are moved on to the next stage of treatment by use of a grit channel that is engineered to generate an optimal flow rate. Primary settling tanks, also known as basic sedimentation tanks, are the unit process for the gravitational separation of solids during sewage's primary

treatment. In addition to domestic wastewater, it is also often used to treat industrial wastewater. When settling basins are at rest, particles that are heavier than water sink to the bottom. Floating oil like soap scum may be skimmed out of a clarifier using a skimming device, along with materials like feathers, wood pellets, or rubber. Oil and water may be kept apart in vessels such as the API oil-water separator.

2) **Biological and chemical processes**

- **Oxidation**

The toxicity of certain contaminants in wastewater may be reduced by oxidation, and the biological oxygen demand of sewage is also reduced. Through reduction and oxidation processes, organic molecules in secondary treatment are transformed into co2, water, and biosolids. As a common method of germ-killing, chemical oxidation is necessary.

- **Biochemical oxidation (secondary treatment)**

Phase separation mechanisms like this compact clarifier at a regional wastewater treatment facility are often used to filter out biological solids produced by a bioreactor with suspended growth or a fixed-film culture. Biodegradable organic material in suspension or solution is removed from wastewater (such as sewage) through a second treatment process called secondary treatment.

The purpose of a wastewater treatment plant is to produce

effluent of a specified grade, one that can be safely disposed of or reused as planned. Physical deformation is often employed as a "primary treatment" stage before secondary treatment to eliminate settled solids. Added and the solution-suspended organic materials, quantified by biochemical oxygen demand, are removed by biological processes during secondary treatment. Microorganisms, in a controlled aerobic or anaerobic environment, perform these functions in water and wastewater treatment. Cells of biological solids are formed when bacteria and protozoa devour biodegradable soluble organic pollutants from human waste, food waste, soaps, and detergents, such as sugars, lipids, and especially organic short-chain carbon molecules. Many types of industrial and agricultural sludges may benefit from secondary treatment, which is why it is so often utilized in sewage treatment.

- **Chemical oxidation**

Some persistent organic contaminants and quantities that remain after biological oxidation are eliminated using advanced oxidation techniques. Chemical oxidation disinfects wastewater by introducing hydroxide ions such as ozone, chlorine, or hypochlorite, which destroy bacteria and microbial pathogens. This hydroxyl radical then decomposes organic contaminants into simpler components like freshwater, CO2, and salts.

- **Anaerobic treatment**

The process of treating industrial wastewater and

biological sludge also makes extensive use of anaerobic wastewater treatment technologies like UASB and EGSB.

3) Polishing

After the aforementioned procedures, the "fourth stage" of therapy consists of polishing. Some types of industrial wastewater may also benefit from these treatments on their own. Wastewater that has undergone chemical oxidation may have its chemical reactivity reduced by undergoing a chemical reduction and pH adjustment. Activated carbon filters use chemical absorption to get rid of any lingering pollutants or impurities. The majority of municipal wastewater is filtered by sands (calcium carbonate) and fabric filters.

2.6. Sludge Treatment, Utilization, and Disposal

The term "sewage sludge treatment" is used to describe the procedures that are implemented to deal with the waste product of the sewage treatment process. The goals of sludge treatment include minimizing the possible health concerns associated with disposal methods and lowering the sludge's weight and volume for cheaper transportation and disposal. Pathogens may be killed using heat through methods like thermophilic digestion, composting, or burning, whereas weight and volume can be reduced mostly by the elimination of water. It is important to consider the amount of sludge that will need to be treated and to weigh it against the expense of other disposal methods before settling on a course of action. Cities may

favor aerobic digesting as well as mechanical dewatering because of limited land availability, whereas rural locations may find air-drying and composting more appealing due to economies of scale.

To create sludge, liquid sewage is treated to remove most of the solids, leaving largely water. Settleable solids collected in primary clarifiers are considered part of the primary sludge stream. Sediment collected in a secondary clarifier and afterward employed in a bioreactor or a procedure involving inorganic oxidizing agents is referred to as secondary sludge.

Because the tanks in the liquid line cannot contain the sludge generated by intensive sewage treatment procedures, the sludge must be continuously evacuated from the liquid line. This is done to maintain a steady and compact treatment procedure where the production of sludge is approximately equal to the removal of sludge. When the sludge is drained from the liquid line, it is transferred to the sewage treatment connection.

In general, more sludge is produced by aerobic processes than by anaerobic ones. In contrast, the sludge generated in large (natural) treatment procedures like ponds and manmade wetlands accumulates in the treatment facilities and is only eliminated after many years of operation.

The alternatives available for treating sludge are contingent upon the number of solids produced in addition to other site-specific factors. Smaller plants often

use composting, whereas medium-sized businesses use aerobic digestion, and large-scale businesses employ anaerobic digestion. In certain cases, a "pre-thickener" is used to remove excess water from the sludge. Pre-thickeners might be anything from a belt filter press to a rotary drum sludge thickener to a centrifugal sludge thickener. Sludge that has been dewatered may be burned, taken elsewhere, and disposed of in a dump or used as a fertilizer additive on farms.

The energy yield from sludge is often inadequate to evaporate the sludge water content or to electricity blowers, pumping systems, or filtration required for dewatering, even though energy can be retrieved from wastewaters and via methane gas production throughout anaerobic digestion or by incineration of dried sludge. Toxic compounds that have been absorbed by solid materials in clarifier sludge are likely to be found in both coarse main solids as well as secondary wastewater sludge. Some of these harmful substances in the sludge may become more concentrated if the volume of the sludge is reduced.

2.6.1. Treatment processes of Sludge sewage

Sludge produced during the treatment of wastewater should be properly managed and disposed of. Raw sludges are digested in many huge factories, which reduces their volume.

1) Thickening

Sludge treatment procedures often begin with thickening. When clarification chemicals are added to sludge in a secondary or primary clarifier, stirring the sludge may help it form a bigger, faster-settling aggregate. It is possible to thicken primary sludge to 8 - 10% solids and secondary sludge to 4% solids. A thickener is a clarifier with a stirring device added. Subsequent sludge processing may be applied to thickened sludge containing less than 10% solids, while the excess from the thickener is recycled back into the wastewater treatment system.

2) Dewatering

Sludge's excess water may be decreased by centrifuge, filtering, and evaporation to lower disposal transportation costs and increase its compostability. To prepare sludge for future filtering or evaporation, centrifugation is sometimes used as a first step. Sands drying beds with problems need to be addressed do filtration, as does the mechanical belt filter press. The filtration and centrifugation byproducts of wastewater treatment are frequently recycled. Dewatered sludge typically contains between 50 - 75% water, making it manageable as a solid. Relatively highly dewatered sludges are often treated as liquids.

3) Digestion

Most sludge goes through some kind of digestion process, the goal of which is to decrease the quantity of organic

material as well as the amount of disease-causing microbes in the solids. Anaerobic treatment, aerobic digestion, as well as composting are the three most frequent methods of waste management. When compared to traditional sludge disposal methods, sludge digestion's cost savings come from its ability to cut sludge production by almost half while also producing usable biogas for power generation.

Digestion's end goal is to lessen the solids' organic content and microbial load, both of which may cause illness. Methane gas, produced in this way, may be used as energy to operate the facility or sold to other businesses.

- **Anaerobic digestion**

Lack of oxygen during bacterial digestion is known as anaerobic digestion. Sludge is digested in tanks at temperatures between 55 and 36 degrees Celsius in either the thermophilic or mesophilic digestion process. Thermophilic digestion is more costly since it requires heating the sludge, allowing for less retention time and thus smaller tanks.

Thermophilic digestion is much more costly because of the energy required to heat the sludge, even though it allows for a shorter retention period and consequently smaller tanks.

Sludge from sewage treatment facilities may also be processed via Mesophilic Anaerobic Digestion (MAD). Feeding the sludge into enormous tanks, where it will

remain for at least 12 days, allows the process of digestion to complete its four phases. To name a few: hydrolysis, acidogenesis, acetogenesis, as well as methanogenesis. Through this process, complex molecules like proteins and carbohydrates are converted into simpler ones like H2O, CO2, and CH4.

The methane-rich biogas produced by anaerobic digestion may be utilized for both tank heating and to power on-site machineries like motors and microturbines. The production of methane is one of the many benefits of anaerobic treatment. Its primary drawback is the costly initial investment and the lengthy processing period (up to 30 days).

- **Aerobic digestion**

An aerobic digester uses bacteria to break down organic matter in the atmospheric oxygen, much like the activated sludge method but without the need for chemicals. In an aerobic environment, bacteria devour organic materials quickly and release carbon dioxide. When food sources dry up, germs die off and are eaten by survivors. Endogenous respiration describes this phase of the procedure. This is the stage when the solids are diminished. Aerobic digestion has cheaper startup costs than anaerobic digestion since it produces results more quickly. Aerobic digestion often has higher operational expenses than anaerobic digestion due to the energy required to run the blowers, pumps, and motors involved

in oxygenation. Aerated filter devices that rely on natural air currents rather than electrically controlled equipment are one example of a recent technical development.

Diffusion pumps or jet aerators may be used to oxidize the sludge, resulting in aerobic digestion. Although fine bubble diffusers tend to be the most cost-effective option, they often get clogged as silt settles into the tiny air holes. In activated sludge containers or during the flocculation phases, coarse bubbles diffusers are more typically utilized. Making sure the diffuser type you choose can provide the necessary oxygen transfer rate is crucial.

4) Sidestream treatment technologies

The thickened as well as dewatered sludge and the liquid fraction also termed sludge treatment liquid, sludge dewatering rivers, distilled spirits, centrate if it originates from a centrifuge and filtrate if it originates from a belt filter press are the two products of sludge treatment methods. Especially if the sludge has indeed been anaerobically digested, the resulting liquid will be rich in nitrogen and phosphorus and will need further treatment. The procedure may happen at the wastewater treatment plant by reusing the liquid at the beginning of the treatment process, or it can happen separately.

- **Phosphorus recovery**

Sludge dewatering rivers may be treated using a procedure that is also utilized for phosphorus recovery.

Reduced production of obstructing crystal formatting scale in pipelines, compressors, and valves is another advantage of processing sludge dewatering channels for phosphorus recovery for wastewater treatment plant operators. When the phosphorus concentration in sewage sludge is high, such obstacles may be a maintenance nightmare for biological fertilizer removal units.

5) Composting

Combining sewage sludge with carbon sources from agricultural byproducts like sawdust, hay, or wood is called composting, and it's an aerobic process. Bacteria digesting the wastewater sludge and plant material produce heat, which is used to destroy disease-causing microbes and parasites, provided that oxygen is present. Bulking agents, which enable air to move through the fine-activated sludge, are necessary for keeping aerobic conditions with between 10 and 15 percent oxygen stable. Leaves and grass clippings are not as effective in separating sludge as harder materials like cereals, nut shells, shredded branch waste, or waste from wood or paper mills. Where tiny, soft plant components are the primary source of carbon, light, inorganic bulking agents like chopped tires may be utilized to create structure.

Placing an insulating covering of composted sludge over aerated composting heaps may help with the homogenous distribution of pathogen-killing temperatures. The compost mixture should have an initial moisture level of about

50 percent, however, in cases when wet sludge or rainfall boosts compost moisture content to 60 percent, temperatures may be insufficient for pathogen elimination. A layer of undifferentiated bulking agents may be placed on top of composting mixes stacked on concrete platforms with integrated air ducts. An aerating compressor may be used to pull suction through the composting pile through the underneath ducts and then expel the air through the use of filtration piles of previously composted sludge, which is then replenished when the moisture content of the pile reaches 70%, so reducing odors. Composting pads may have roofs installed to better regulate moisture content, and liquid that collects in the beneath drain ducting can be sent back to the wastewater treatment facility.

Compost heaps may be filtered to retrieve unprocessed bulking agents for reuse after a period of composting long enough to kill off pathogens, and the decomposed solids that make it past the screen can be utilized as a soil amendment product with advantages comparable to peat. However, the composting proportion of agriculture leftovers may be chosen by the quantity needed to dilute concentrations of harmful chemicals in the sludge to tolerable levels for the desired compost usage, rather than the ideal carbon-to-nitrogen ratio of 26-30:1. Grass clippings from the suburbs may include residual pesticide levels that are harmful to certain agricultural purposes, and newly composted wood wastes may contain

phytotoxins that impede seedling germination until detoxed by a soil fungus.

6) Incineration

The practice of burning is also used but to a considerably smaller extent. Air pollution concerns and the additional fuel usually natural gasoline or fuel oil needed to burn the low energy content sludge and vaporize leftover water have reduced the frequency with which sludge is incinerated. The two most frequent methods for incineration of wastewater sludge are the high-residence-time, stepped-multiple-hearth incinerators, and the fluidized-bed incinerators.

Municipal waste-to-energy plants may engage in co-firing, a cost-effective strategy if enough solid waste facilities already exist and no supplementary fuel is required. Maximum concentrations of heavy metals in the residual solid ash after incineration are a major disposal issue, but the alternative of returning wet wash cloth effluent to the water and sewage process has the potential to lower air pollutants by increasing the number of dissolved solutes in the effluent from the water treatment facility.

7) Drying beds

Drying sewage sludge in simple sludge treatment beds is a common practice in many nations, especially in poor countries due to the low cost and ease of the process. It is important to collect drainage water, and although drying

beds are occasionally covered, they are often kept uncovered. There are additional mechanical devices on the market that may be used to mix the sludge during the preliminary drying phases.

Standard drying beds include four layers of sand and gravel. The first 15–20 cm is comprised of gritty gravel. As a filter between both the muck and the pebbles, the third layer of sand sits at a depth of 10 to 15 cm. underneath everything, sludge dries out, and water filters down to the first layer, where it is gathered at the drainpipe.

2.6.2. Disposal or use as fertilizer

Additional processing may be needed to make the liquid sludge generated ready for disposal. To decrease the amount of sludge that must be hauled away for disposal, it is common practice to thicken and/or dewater the sludge beforehand. Lagoon in drying beds results in a block that may be applied to land or burnt; pressing involves physically filtering sludge, usually using fabric screens, resulting in a solid cake; and centrifugation thickens the sludge by dividing the liquid and solid phases. Landfills and liquid injections onto land are two options for pollutant removal. Unfortunately, there is currently no method that can do away with the necessity for treated sewage sludge disposal.

Toxic elements from both commercial and industrial activities, as well as those from private households, contaminate a significant portion of the sludge that is

produced in commercial and industrial zones. Sludge with a high concentration of these substances may be unfit for agricultural use and end up being burnt or dumped in a landfill. Applying sewage sludge to farmland is still a popular choice, even if part of it may not be fit for use.

2.7. Nonpoint Source Water Pollution

Discharge from land, rainfall, industrial emissions, drainage, leakages, and hydrological change are common sources of NPS contamination. When compared to pollution from factories and sewage treatment facilities, NPS pollution originates from a wide variety of centralized sources. Pollution in NPS occurs when precipitation or snowmelt percolates into the ground. Naturally occurring and anthropogenic pollutants are picked up by the runoff as it travels and eventually dumped into bodies of water such as lakes, streams, wetlands, shorelines, and underground water.

2.7.1. Characteristics of nonpoint sources:

- Pollution from agricultural runoff caused by irrigation and the use of chemicals and fertilizers
- The drainage of pastures and rangelands
- Flows of water from cities that don't have sewage systems
- Liquid waste from a septic tank
- Surface water from building projects larger than 20,000 square meters

- Mine drainage
- Particles fall from the atmosphere and land on a body of water.
- Alternative pollutant-releasing Land use activities

Water contamination from several, dispersed sources that can't be traced back to a single culprit is notoriously tough to control. The widespread nature of activities that contribute to nonpoint source water pollution—including fertilizing lawns, using pesticides, constructing roads, and constructing buildings makes it challenging to mitigate. To reduce the effects of nonpoint source pollution, we need to do a better job of overseeing our cities and suburbs, farms and forests, and harbors.

Sediment, fertilizers, hazardous pollutants and chemicals, and pathogens all fall under the category of non-point source water pollution. Urban as well as suburban areas, agriculture activities, meteorological inputs, highway overflow, forest and mining processes, marinas as well as marine activities are all significant contributors to nonpoint source water pollution. Metropolitan runoff refers to polluted stormwater that drains from impermeable surfaces like parking lots, roadways, and highways in urban areas. Non-point source water contamination occurs when nitrogen compounds seep off of fertilized agricultural soils. Stormwater pollution that carries excess nutrients from a nearby field or forest is another kind of non-point pollution.

Nonpoint source pollution can include:

i. Pollution from farms and homes that use too much pesticide, herbicides, or insecticides
ii. Urban runoff as well as power generation is a major source of oil, grease, and hazardous substances.
iii. Erosion of stream banks, runoff from unmanaged building sites, fields, forests, and other sources of sediments
iv. Acid runoff from disused mines and salts from irrigation methods
v. Cattle manure, pet waste, and malfunctioning septic systems all contribute to a breeding ground for bacteria.
vi. Hydrologic alterations and industrial emissions

2.7.2. Principal types for Nonpoint water pollution

1) Sediment

Sludge (fine particles), as well as suspended solids, are components of sediment (loose soil). Erosion of stream banks and surface runoff from unsuitable plant cover on both urban and rural terrain may contribute sediment to water bodies at the surface. When sediment settles on the surface of a body of water, it causes turbidity, which reduces the amount of sunlight that reaches deeper layers. This has the potential to stunt the development of subsurface aquatic plant life which in turn might have negative effects on fish and shellfish populations. Water

treatment processes are hampered by excessive turbidity.

In addition, a wide variety of facilities can release sediment. In addition to building sites (which are point sources that may be controlled with erosion management and sediment controls), other sources include farmland, stream banks, and severely disturbed landscapes.

2) Nutrients

Discharge, dumps, animal activities, and agricultural fields all provide inorganic material that is considered a nutrient. Phosphorus and nitrogen are the two most critical nutrients.

Phosphorus is an essential nutrient that may be found in many different forms that are digestible by the body. Human sewage sludge is quite plentiful. It is a key component of many fertilizers applied to farms and lawns, and it has the potential to become a scarce resource in freshwater ecosystems and some estuaries. Many kinds of phosphorus prefer to be deposited on soil particles, making soil erosion a major pathway for phosphorus to enter water bodies. Microorganisms, tiny algae, proliferate when there is an excess of phosphorus in freshwater environments, especially in fresh waters, dams, and ditches. Nutrient enrichment refers to an increase in the availability of organic matter owing to the excessive development of plankton. The growth of algae is a frequent sign of eutrophication; they may discolor the water's surface, block out sunlight for beneficial plant

species, alter the water's flavor and odor, and even poison the water with their poisons. Some of these pollutants may make people sick, making them a serious concern in water systems that people use to drink. Furthermore, getting rid of these poisons is difficult and costly. Fishes as well as marine mammals suffer when the dissolved oxygen level in the water is depleted due to the bacterial breakdown of algal blooms.

In saltwater or saline estuary environments, where nitrogen is an essential micronutrient, nitrogen, another essential element in fertilizers, often becomes a contaminant. Eutrophication and algal blooms are caused by an abundance of accessible nitrogen in oceans, just as they are by an abundance of phosphorus in freshwaters. Wide swaths of the estuary, ports, and near-shore coastal waters may be affected by hypoxia as a consequence of nutrient enrichment in marine systems.

Nitrate(NO_3) is the most prevalent form of nitrogen carried by water. As natural or ammonia (NH_3) is often used to supplement a watershed, the nitrogen remains bound to the soil unless oxidation transforms it into nitrate. Since nitrate is often already present in the soil, it is more likely to be carried by water that moves through soil i.e., interflow and tile drainage than by runoff water.

3) Toxic contaminants and chemicals

Several compounds are immune to degradation, including heavy metal ions like mercury, cadmium, and lead, as well

as zinc, organic material like polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), and fire retardants. Human wastewater, mining activities, car emissions, fossil fuel burning, urban runoff, industrial plants, landfills, and so on are all potential sources of these toxins.

Organic molecules and inorganic compounds are the most common types of toxic substances. Chemicals like DDT and other pesticides, acids, and salts have devastating impacts on aquatic life and the surrounding environment. Because of their resistance to environmental breakdown, these chemicals may linger in the environment and pose harm to human and aquatic health. Farmland, nursery, orchards, construction sites, gardens, meadows, and landfills are all potential sources of these harmful substances. Inorganic pollutants such as acids and salts come from sources such as irrigated fields, mines, urban runoff, factories, and landfills.

4) Pathogens

Human illnesses are caused by pathogens, which include viruses and bacteria that may be found in water. When microorganisms are prevalent in municipal water systems, they often spread illness. Polluted rainwater may contain pathogens such as:

- Parasitic Yeast, Cryptosporidium Partum
- A lambda bacterium called Giardia
- Salmonella

- Viruses, including the Norwalk virus
- Hookworms and other parasitic worms

Water that has been through a storm drain has the potential to include feces and coliform germs. Although they are often used as a proxy for water contamination, the bacteria in question do not directly cause illness.

Runoff might be tainted with pathogens if cattle activities weren't handled properly, septic systems weren't maintained, pet waste wasn't properly disposed of, human wastewater was spread in excess, storm sewers were polluted, and sanitary sewers overflowed.

2.7.3. Principal sources for Nonpoint water pollution

1) Urban and suburban areas

Because of the large quantity of runoff created by the vast number of pavements, urban and suburban regions are major contributors to nonpoint source pollution. Water cannot penetrate paved surfaces such as concrete or asphalt. Water that makes touch with these substances will evaporate or be consumed by the environment. They facilitate the transport of contaminants into the soil via runoff. The soil at construction sites is often disturbed, making it vulnerable to erosion during wet weather. Furthermore, litter from the location might be washed away by runoff waters, polluting nearby bodies of water.

The term "urban runoff" is used to describe polluted rainwater that drains off of urban surfaces including

parking lots, roadways, and lawns. It is common practice to label this outflow as NPS contamination. Since it is often directed into municipal stormwater drainage systems and then emptied through pipes into neighboring surface waterways, this phenomenon may be also a point source. However, not all water from cities is collected by storm drains before it reaches bodies of water. Especially in urban and suburban settings, some may find their way straight into bodies of water. Contamination in urban runoff could not be traced back to a single source or even a cluster of sources as other kinds of point sources can, such as industrial effluents, wastewater treatment facilities, and other activities. Therefore, urban runoff contamination sources are generally viewed as genuine nonpoint sources when municipalities seek to abate them since they are not created by a readily defined and controlled activity.

Most suburban lawns are treated with chemical fertilizers and pesticides. Some of these chemicals may make their way into the environment via the city's storm drains and other runoff. Chemicals are introduced directly into water sources because storm drain water is not purified. Changes to the environment and forest management are also major contributors to runoff (forestry).

2) Agricultural operations

Industrial fertilizer, animal wastes, and the spraying of industrial or municipal wastewater or sewage are common methods for introducing nutrients to agricultural land.

Crop leftovers, irrigation water, animals, and air deposition are all potential sources of nutrients in waterways. A kind of agricultural pollution is sediment (loose dirt) splashed from fields. Factories, which raise vast quantities of animals and poultry, are a common kind of farm that acts as a point source discharger. Intensive animal feeding operations, sometimes known as "feedlots," is the common term for these establishments.

Non-point source contamination in many countries is mostly caused by agricultural activities. Growing crops over vast swaths of land uncovers and aerates previously hidden soil. Because of this, the uncovered soil is more likely to be washed away by rain. The quantity of fertilizer and chemicals washed into local water sources may also raise.

3) Atmospheric inputs

The transfer of natural and inorganic elements from air pollution sources to ground-level receptors makes atmospheric deposition a source of these compounds. Most manufacturing facilities, including smokestacks, contribute to air pollution. Even though this is a prime source, it may be treated as a non-point source origin in the depositional region because of its dispersed character, long-distance transport, and many sources of pollution. The quality of runoff may be affected by both wet and dry deposition from the atmosphere during and between storms. Uncertainties in the number of different air sources

in runoff are caused by the impact of motor activity on the dry and wet depositing that happens on or near roads, roadways, and parking spaces. Unfortunately, networks that employ standards adequate to quantify that concentration and burdens do not monitor many of the elements of concern, and they are too dense to offer reliable deposition estimations at the small level.

4) Highway runoff

Highway discharge is a very minor contributor to nonpoint source pollution, yet it has far-reaching effects. According to research runoff loads were made up of 9 percent air fallout, 25 percent vehicle deposition, and 67 percent road maintenance components. And it was also estimated that nine percent of those loads were re-released into the air.

5) Forestry and mining operations

Non-point source contamination may be exacerbated by activities like logging and mining.

i. Forestry

Cutting down trees for logging purposes has the negative side effect of decreasing the amount of oxygen in the air. This behavior, along with the movement of harvesters and other heavy gear, heightens the possibility of soil degradation.

ii. Mining

Discharge from defunct mines contributes to non-point source pollution, while active mines are considered point sources. For strip mining, the mountaintop must be leveled to get to the mineral. Erosion of the soil may occur if this region is not adequately recovered once mining has ended. Furthermore, air and the exposed rock may undergo chemical reactions, leading to acidic discharge. Subterranean mines that have been abandoned often leak extremely acidic water into the surrounding environment. Seeping into the nearby body of water may alter the pH balance of that ecosystem.

6) Marinas and boating activities

Boat maintenance substances such as paints, cleaners, and lubricants end up in waterways via runoff. Boats are another contributor to non-point source pollution because of fuel spills and leaks. Unsanitary waste receptacles aboard the boat as well as at pressure regulator stations raise nutrient as well as bacterial levels.

2.7.4. Control ways for Nonpoint water pollution

1) Urban and suburban areas

Both in urban as well as suburban settings, a wide variety of measures may be done to curb nonpoint source pollution. Grassy buffer strips separate hardscapes like parking areas and roadways from nearby water sources. This gives the soil time to process any pollutants before it

reaches the water supply. To prevent water contamination from stormwater runoff, retention ponds may be constructed in low-lying locations. The retention pond is designed to receive runoff and stormwater, where the pollutants may settle to the bottom and be retained. There is less runoff into the water source when the porous pavement is used. Wetlands and other forms of restoration are utilized to reduce runoff and trap pollutants.

Simple steps are routinely used at construction sites to lessen pollution and water runoff. Initially, silt fences or sediment fences are set up around building sites to lessen the quantity of sediment and big debris washing into the nearest body of water. To further limit nonpoint source pollution, grass or straw may be laid around the perimeter of building sites. Local government rules might mandate septic system maintenance in regions serviced by single-family septic systems to guarantee that water quality criteria are met.

2) Agricultural operations

To keep sediments and outflow under control, farmers may use erosion controls to slow down the rate of runoff and keep more of the soil where it belongs. In agriculture, common practices include contouring pouching, plant mulching, mixed cropping, planting annual crops, and constructing ecological buffers. When sowing a fresh crop, the notion of conservation tillage is used to lessen the amount of water lost to the environment. When planting, a

farmer would often leave behind part of the agricultural residue from the previous season to slow down the rate of runoff.

Industrial fertilizer, animal wastes, and the sprinkling of municipal or commercial sewage or sludge are the most common methods of introducing nutrients to agricultural land. Crop leftovers, irrigation water, animals, and air deposition are all potential sources of nutrients in waterways. Farmers may curb the overuse of nutrients by creating and implementing nutrient management programs.

To keep pests under control, use fewer chemical pesticides, and safeguard water quality, producers may employ Integrated Pest Management (IPM) strategies which might include biological pest management.

3) Forestry operation

Logging tracks, sometimes known as skid trails, may have a less negative impact on the environment by being strategically placed. Loose silt in runoff may be minimized by situating trails as far as feasible from active logging areas and by shaping paths to follow natural terrain features. Trees planted in their place after logging help the soil recover its stability and restore the original ecosystem.

4) Marinas

Gasoline spillage may be mitigated by installing a shutdown valve on fuel stations at a port terminal.

Furthermore, sailors may find a clean location to discard sewage that is not water by using pump-out facilities that are conveniently located in a port. The presence of trash cans near a port is one easy solution to the problem of huge rubbish being thrown into the sea.

2.8. Water Pollution Law and Regulations

Indian Laws and Acts to reduce Water Pollution:

- In 1882, Congress passed the Easement Act, which recognized groundwater as an appurtenance to the property and thereby protected private rights to its usage. All groundwater is also considered state ownership, according to the document.
- Using explosive charges or any other explosive material in any manner (regardless of whether coastal or even inland) intending to capture or eliminate any fish and perhaps even poisonous fish to kill is illegal under both sets of penalties established by the Indian Fisheries Act of 1897.
- To address problems with interstate collaboration, the states may petition the federal government to establish an Advisory River Board according to the River Boards Act of 1956.
- In 1970, Congress passed the Merchant Shipping Act to address the issue of marine debris along the shore within a certain distance.
- The Water (Prevention and Control of Pollution) Act of 1974 creates a regulatory framework for

reducing water pollution. It sets requirements for the cleanliness of the water and wastes discharge. Polluting industries are required to obtain a permit before dumping their waste in bodies of water designated as effluent. Under this law, the Central Pollution Control Board (CPCB) was established.

- The Water (Prevention and Control of Pollution) Cess Act of 1977 allows for the imposition and collection of cess or fees from industries and local governments that use significant quantities of water.
- The Water (Prevention and Control of Pollution) Cess Rules of 1978 define key terms and specify where and what kind of water meters must be installed for all residential, commercial, and industrial users.
- Construction is one of many activities that are restricted by the Coastal Regulation Zone Notification of 1991. Some of the estuaries and backwaters are shielded.

Some main Acts of water pollution are:

1. **Water Prevention and Control of Pollution Act, 1974**

To prevent and control water pollution and preserve or restore water's purity, the Water Act of 1974 was adopted. To achieve these goals, it mandates the creation of water pollution prevention and control boards. The Water Act

forbids and provides sanctions for, the release of contaminants into water bodies over a certain level. The CPCB was established under the Water Act to provide national guidelines for the mitigation of water pollution. The CPCB and the State Government are responsible for overseeing the operations of the SPCBs at the state level.

Additionally, a cess on water use by those running and carrying out certain sorts of industrial operations was established in 1977 under the Water (Prevention and Control of Pollution) Cess Act. The goal of this cess is to provide more funding for the Central Board and the State Boards for the control and prevention of water pollution established under the Water (Prevention and Control of Pollution) Act of 1974. In 2003, an update was made to the law.

- **Relevance of Section 24 of this Act**

Section 24 of the Act mandates that no person may cause or let any dangerous or noxious waste, as defined by the criteria set out by Central Pollution Control Board, enter or remain in any stream, sewer, or land. No person may deliberately enter any stream in such a way as to obstruct the natural flow of water or create pollution of water, as this Act imposes on the person. Any person who breaches or contravenes the provisions of this Section will be subject to a penalty of imprisonment for a term of one year as well as six months, which may extend to a term of six years.

- **Drawbacks of this Act**

Despite being one of the early statutes which were being approved by the Indian Parliament to regulate the pollution of water, the Water Pollution Prevention and Control Act suffers from several problems. The lack of groundwater management policies is a major flaw in this Act. Another flaw of this Act is that it fails to address issues like the wasteful use of groundwater, rainwater collecting, etc.

2. The Shore Nuisance Bombay and Kolaba Act

The legislation was passed to make it easier to clean up areas of Bombay and Kolaba that are below their respective high water marks. The act's stated purpose was to prioritize the public interest and ensure the safety of navigation in Bombay Harbor. The property tax collector of Bombay is authorized to issue a summons to clear any impediments or nuisances that are below the mean high water mark according to the Act. Posting the notice in a visible location, either near the obstacle or the harbor at low tide, is the accepted method of delivering such a warning. If the notification is not responded to within 1 month of issue, a competent body in the state is authorized to remove the impediment. Fines for violating the act's provisions on water pollution may be used as a measure to evaluate its efficacy.

3. Orissa River Pollution Act, 1953

Among the major causes of water pollution in India is the

improper disposal of garbage. The companies and industries of the nation are the primary sources of waste that contribute to the river's pollution. The goal of this law is to keep rivers and streams in good condition by limiting the amount of industrial waste and effluents that may be dumped into them. The government of Orissa formed the aforementioned board to administer the Act and ensure its effective implementation. The authority to speak for the people of a certain area has been granted to the board by this statute.

The water contamination situation in Orissa has to be brought under control immediately. Recent research on water pollution has shown that the Mahanadi and Brahmani rivers in Orissa are among the most contaminated in the country. These rivers have filthy water that makes it difficult for humans to live. Major sources of pollution in Orissa include sewage, trash from industry and mining, and the improperly disposed of toxic substances like lead as well as magnesium.

4. **The Water Prevention and Control of Pollution Cess Act, 2003**

Water contamination may have several origins, one of which is industrial waste. Industries often dump their trash into waterways, thus contributing to river pollution. Section 2 of this Act defines "industries" to encompass any activity that generates wastewater, whether from a household or a commercial establishment. Companies

whose water use is below the threshold established in Section 3 of this Act are exempt from paying the cess required of other companies. Under this rule, businesses that release harmful or non-biodegradable compounds into the water supply during the production of these commodities are liable to pay a cess.

5. **The River Boards Act, 1956**

The goals of this law were to create rivers and settle water issues between states. This Act's primary focus is on protecting the public interest. The State Government may create Boards by making a specific notice under the authority of the Act. This Act's goal is to control and settle the water conflicts between states. It is the responsibility of the Union to create and resolve the inter-state water conflicts that exist in India, according to Article 262 of the Indian Constitution. The purpose of this Act was to establish national courts and awards to govern the resolution of international disputes inside a given country.

6. **Damodar Valley Corporation Prevention of Water Pollution Act, 1948**

Ever since the beginning of recorded history, the Damodar Valley has experienced one of the highest rates of river basin prosperity in the nation. Damodar Valley Corporation was formed to monitor the activities in this valley. Eighty percent of the garbage from mines and industry is dumped into this river during the monsoon season. In the wake of such Cooperation, the agriculture

industry has experienced significant transformation. From 1925 to 1984, agricultural land shrank from 59% to 10%. During that time, the mining sector was very important. These miners used this river to dispose of their waste products. When this happens, water contamination occurs.

Right to Clean Water: a Fundamental Right

To reduce water pollution, the Indian judicial system has taken a promising new initiative. The Indian court has liberally interpreted Article 21 of the Indian Constitution, expanding its scope to encompass the rights to clean water as well as the environment under Articles 21, 48, and 51(g). The overarching notion of a Right to Life has its roots in several landmark legal judgments that have been made all through the course of Fundamental Rights. The court has argued that the entitlement to clean water is part of the fundamental right to life, and as such, it falls under the purview of Articles 21, 48, and 51(g) of the Convention. The Supreme Court of India ruled that access to clean water is a basic right protected by Article 21 of the Indian Constitutional in the case of Narmada Bachao Andolan. The right to clean water was recognized by the court as an integral component of the right to life. The government has a responsibility to safeguard the water supply. The Supreme Court of India has ruled that protecting the purity of the Ganges River is an urgent matter, citing the landmark decision of MC Mehta vs. The Union of India.

There is an immediate need to avoid the contamination of

our rivers, dams, streams, and ponds, although the Parliament has approved various acts to limit water pollution. Storage tanks, rivers, and lakes should all be monitored by the government, and a watchdog group should be set up to ensure that the government is doing its job.

The Indian Penal Code and Pollution

The criminal law of India has specific measures for punishing those who break the law in a way that goes against the Indian Penal Code. Anyone who knowingly fouls a public reservoir or spring is subject to a three-month jail sentence and/or a 500 Rupee fine, or both, according to Section 277 of the Code. An example may serve as the key to unlocking the meaning of this scenario. A citizen of Chandigarh, 'A' knowingly and intentionally pollutes the water supply by placing a harmful material near a reservoir. Before A, the reservoir was suitable for public use; after A, it is no longer suitable for such usage. A was found guilty under Section 277 of the IPC and sentenced to up to three months in jail and a fine of 500 Indian Rupees.

2.9. Types of health issues

Diarrhea, dysentery, cholera, chronic hepatitis A, malaria, and poliomyelitis are just some of the illnesses that may spread due to a lack of clean water and proper sanitation. People face avoidable dangers to their health when access

to safe water and sanitation is lacking, poorly managed, or nonexistent.

Pollution is more closely linked to health issues than most people realize. Pathogens are bacteria that cause illness, and they are transmitting that sickness directly to people. Some diseases may be found everywhere in the world, while others are confined to certain regions. Humans are the vector for the transmission of many water-borne illnesses. Extreme weather, such as hurricanes, tornadoes, and monsoons, is a leading cause of new illnesses in both industrialized and developing nations. Produced in polluted water supplies, 10% of the population relies on it. The fecal-oral channel of infection is associated with many aquatic infectious illnesses, which is a direct outcome of fecal contamination of water sources. Diseases ranging from respiratory to cancerous to diarrheal to neurological and cardiovascular are all linked to drinking water that is contaminated with pollutants.

Cancer as well as blue baby syndrome are both linked to exposure to nitrogenous pollutants. Because individuals in cities have easier access to clean drinking water, the cancer death rate in rural regions is disproportionately higher. Due to a lack of access to clean water, good sanitation, and basic hygiene, the poor are disproportionately affected by the spread of illness. Women who drink contaminated water while pregnant are at higher risk of having babies with low birth weights because of the toxins in the water harm the developing fetus.

Poor water quality is harmful to aquatic organisms and human life because it damages agricultural productivity and infects our food. Heavy metals, notably iron, disrupt the food chain and harm the respiratory systems of fish. The consumption of fish that have had their gills clogged with iron is a big public health concern since it causes fish poisoning in humans. Hair loss, cirrhosis of the liver, kidney failure, and neurological dysfunction are all caused by metals in water.

1. **Bacterial diseases**

The most common cause of diarrhea is water contamination by human feces or the usage of untreated water. Campylobacter jejuna are responsible for 4- 15% of all cases of diarrhea. In addition to diarrhea, primary symptoms might include a high temperature, stomach discomfort, nausea, and headache. This illness is preventable with clean living conditions and the use of antibiotics. The cholera epidemic is a direct result of water contamination. Cholera is caused by the bacterium Vibrio cholera. In the digestive system, this bacterium creates poisons. In addition to nausea and vomiting, this illness is characterized by watery stools. Drugs that target microorganisms are used to cure the ailment.

The Shigella bacteria are the culprits in the development of the illness known as shigellosis. It causes harm to the intestinal lining of people. Symptoms include diarrhea (both watery and bloody), cramping in the abdomen,

vomiting, and nausea; treatment with antibiotics and improved hygiene is effective. Salmonella is a bacterial infection that causes diarrhea. Salmonella is a bacterium that may be found in water that causes severe intestinal irritation and, in extreme cases, death. Treatment for this illness often involves the use of antibiotics.

2. **Viral diseases**

Hepatitis is an infection of the liver brought on by a virus that may spread via tainted water. Hepatitis symptoms include jaundice, anorexia, lethargy, nausea, and high fever. If left untreated over an extended period, it might be deadly. Hepatitis is preventable with a vaccine and easily avoidable with clean habits. Inflammatory encephalitis is transmitted by the bite of an infected mosquito. The Culex mosquito only lays its eggs in water that has been tainted. Headache, high temperature, muscular stiffness, convulsions, and, in rare circumstances, coma and paralysis are among the symptoms; nevertheless, most patients exhibit no symptoms at all. There is currently no vaccination for this illness.

The poliomyelitis virus is responsible for this disease. Poliomyelitis may cause a throat infection, fever, uneasiness, diarrhea, constipation, and in rare cases, immobility. This illness has a vaccine. Rotaviruses, adeno-associated viruses, caliciviruses, and the Norwalk virus are some of the viruses that may cause gastroenteritis. Headache, nausea, and stomach pain are all signs of gastroenteritis. The infected individual will begin to show

symptoms one to two days later. Small children, the elderly, and the crippled are especially vulnerable to the risks posed by illness.

3. **Parasitic diseases**

The protozoan parasite cryptosporidium parvum is responsible for the disease known as cryptosporidiosis. Symptoms include diarrhea, loose or watery stools, stomach cramps, and upset stomach, and the disease is widespread. In addition to triggering stomach cramps, nausea, and vomiting in humans, the cryptosporidium parasite is also resistant to disinfectants and affects the immune system. Entamoeba histolytica, the causative agent of galloping amoeba, attacks the lining of the stomach. There are two distinct stages of this parasite's life cycle: the cyst and the non-cyst. When an infected person drinks water containing cysts, they become infected. Fever, anxieties, and diarrhea with a lot of water are all symptoms.

The World Health Organization estimates that 4 billion people suffer from diarrhea each year, causing 2.2 million deaths. The protozoan parasite Giardia lamblia is responsible for the disease known as giardiasis. Intestinal lining cells are susceptible to damage. Giardia may survive in cold environments and is unaffected by bleach. It's a condition that may affect anybody, although it's often associated with travelers. Patients with giardiasis often experience abdominal distention, flatulence, diarrhea, and a decrease in body mass as a result of the parasite.

Chapter 3

Solid Waste

3.1. Solid Waste Disposal

Waste management refers to the process of removing items from circulation after they have fulfilled their intended function or are no longer needed. The development of vector-borne illnesses like rodent and insect-borne typhus may be exacerbated by filthy circumstances brought about by inappropriate treatment of municipal solid waste.

Methods of solid waste disposal and management are as below:

1. Open burning
2. Dumping into the sea
3. Sanitary Landfills
4. Incineration
5. Composting
6. Ploughing in fields
7. Hog feeding
8. Grinding and discharging into sewers

9. Salvaging
10. Fermentation and biological digestion

1. Open burning of Solid Wastes

Not a great strategy for today's world.

2. Dumping into Sea

- Only on coastlines is it even a possibility.
- Dumping of trash requires transporting it on barges 15-30 kilometers from the shore.
- Inexpensive to the extreme
- Toxic to the environment

3. Sanitary Landfilling of Solid Wastes

- Direct, inexpensive, and efficient
- The depth of the trench is between 3 and 5 meters.
- Garbage is stacked like piles.
- Some heavy equipment is used to compact the soil layers before they are protected with more soil, leveled, as well as compressed.
- After some period, the fill would level off.
- Microscopic organisms break down organic substances through chemical reactions.
- The process of decomposition is analogous to composting.
- Organic compounds are broken down by transcriptional bacteria into more manageable,

water-soluble compounds.

- Because of the presence of oxygen, they are converted into carbon dioxide as well as water by soil fungi and bacteria.
- The methane is consumed by aerobic methanogen bacteria, with the remainder diffusing into the atmosphere.
- The danger of starting a fire by burying too much trash.
- Aim for a moisture level of 60 percent or above to ensure proper biodegradation.
- When the depth of the refuse pile exceeds three meters, there is a risk of fire caused by the compression of the lower layers.
- Standard garbage cans have a 2-meter depth restriction.
- As the breakdown process begins, the temperature rises to as higher as 70 degrees Celsius before gradually falling.
- It's possible to repurpose reclaimed land.

4. **Engineered Landfills of Solid Wastes**

- To stop wastewater from seeping into the ground and damaging water supplies, the tunnel bottom is coated with an impermeable substance.
- To properly collect leachate, a system that is both well-designed and -laid out must be supplied.
- The resulting liquid is cleaned up and discarded.

5. **Incineration of Solid Waste**

- A strategy that works well with waste that can be set ablaze
- Waste material is incinerated.
- Excellent for use in dense urban areas where there are no suitable landfills
- Prohibitive building and running expenses
- Waste-to-energy plants are sometimes utilized to lessen the amount of trash sent to landfills.
- The first chamber is designed to ensure that all garbage is completely burned and that any moisture is evaporated quickly.
- For this reason, a shelf or drying fireplace has been constructed.
- Temps over 700 degrees Celsius may be found in the secondary chamber, which is located between the main chamber and the stacks.
- Here, we incinerate anything that wasn't already burned.

i. **Waste to Energy Combustors**

- Particulate emissions control using electrostatic precipitators is hindered by incinerators due to the high intake temperatures produced by the combustion of garbage without energy recovery.
- New combustors recycle energy as they burn garbage.

a) Combustors for Solid Waste

- Recycling center - to store and sort outgoing trash
- Hoist - to load the fuel into the burner
- Enrages at the bottom of a chamber are used for combustion.
- Rough surfaces for trash to slide
- A network of pipes for reusing heat to boil water
- Equipment for dealing with Ash
- Techniques for reducing air pollution
- Grate apertures allow for under-fire air to reach the trash while also moving the trash downward and providing turbulence, all of which contribute to complete burning of the municipal solid waste.
- Combustion systems operate between 980 and 1090 degrees Celsius.

6. Composting

- The same as in enclosed landfills
- Provides a consistent output that can be utilized as a fertilizer basis or as a natural fertilizer.
- Well-liked in the world's poorer nations
- Sorting and composting organic waste is done.

i. **Methods**

- Open window composting
- Mechanical composting

a) **Open window composting**

- Garbage is piled at a height of 1.5 meters and a width of 2.5 meters; the moisture content is about 60%.
- Temperatures in trash heaps may reach around 70 degrees Celsius as a result of biological activity.
- To prevent anaerobic conditions, the pile is rotated for cooling and aeration.
- The relative humidity is lowered to about 60%
- Re-stacked; temperature climbs to a comfortable 70 °C
- The preceding steps are iterated
- Temperature reduces to ambient levels within a few days (7-10 weeks) - a sign of compost stabilization

b) **Mechanical composting**

- Mechanical systems for rotating the composting speed up the stabilization process.
- In a matter of 1–2 weeks, compost reaches a stable state.
- Night soil, cow manure, etc. are often used to enhance compost, along with other types of garbage.
- Typically carried out in a compost bin

- There are drains set up at the pit's base to remove any accumulated water.
- To combat acidity in the composting process and provide an alkaline habitat for microorganisms, a layer of ash, pulverized limestone, or clay loam soil is added there at
- Waste is applied in layers of 30–40 cm in depth and night soil or cow dung is used to fill the hole laid over it in a thin layer.
- About every 5 days, we rotate the stock.
- The preparation period lasts for around a month.

c) Vermicomposting

- Perfect for food scraps, hotel waste, and other biodegradables.
- In the home, a container or tray deeper than 45 cm and measuring 1 x 0.60 m can be all that's needed.
- Liquid waste must be drained into a bucket or other container through a hole in the bottom around one end.
- Sprinkle a 1-inch-thick coating of baby iron or sand into the tray's base.
- On top of the coconut husk, which had been placed upside down, you should place an old gunnery sergeant bag or even a thick piece of fabric, followed by a pile of dry leaves as well as dry cow dung that is at least two inches

deep (powdered)

- Cover it with biodegradable garbage.
- Toss in some quality earthworms (about 10 grams for a box that measures 0.6 by 0.4 by 0.4 meters).
- Every day, if the trash is dry, you should water it.
- To prevent rain from entering the tray, jar, or box, we recommend placing a lid over it.
- Don't open
- Compost may be harvested from the top of the box after earthworms have made their way down from the top of the container and are maintained in direct sunlight.
- It is possible to dry and preserve compost.
- Keep throwing trash into the container.
- Periodically sprinkle on some cow manure.
- Vermiwash should not be used undiluted. Before using, dilute at a 1:10 ratio.

7. **Disposal by Ploughing into fields**
    - Rarely used as a phrase
    - overall unfriendly to the environment

8. **Disposal by hog feeding**
    - Rarely used in India
    - Garbage is finely pulverized in grinders before being flushed down drains.
    - Throwing trash into drains causes a 20-30%

rise in BOD (Biochemical oxygen demand) and TSS (Total suspended solids).

- Refuse disposal is a challenge.

9. **Salvaging**

    - Resources that may be recycled and reused include papers, metals, glassware, rags, some kinds of plastics, etc.

10. **Fermentation or Biological Digestion**
    - Waste that can be broken down into compost
    - Try to reuse as much as you can
    - Appropriately dispose of harmful trash.
    - Throw the remainder out in the trash or burn it

3.2. Reuse, Recycling, and Recovery

Reduction, reused, recycled, and recovery are the four pillars of the 4R Principle, which is extensively used in the field of solid waste management.

1. Importance of the 4R Principle

Among the many reasons why the 4R concept is so crucial are:

- To put the waste to good use.
- To preserve ecological balance.
- So that we can reduce the number of pollutants in our water and soil.

- That's why we need to cut down on wasteful spending.
- To encourage consumers to switch to eco-friendly alternatives.
- Getting the most use out of one's possessions.

2. 4R Principle – Types

The 4Rs refer to the principles of minimizing waste, maximizing reuse, recycling, and reclaiming resources are the following:

a. Reduce:

The term "reduce" refers to any action taken to lessen the amount of trash released into the environment. To avoid relying too much on manufactured items, we should always strive to utilize them only when required. They are:

- The things acquire need to be long-lasting.
- We need to modify our use habits, such as switching to washable clothing and cloth napkins instead of paper ones.
- Pack lunches in easily cleaned containers.
- Use sacks instead of single-use plastic bags.
- Consuming recycled goods is a good idea.
- Cotton shopping bags are preferable.
- Use both sides of the paper when printing to save trees.
- Products should have warning labels detailing proper disposal.

b. Reuse:

Reuse refers to the process of putting a thing to another use without altering its original structure or materials. Repurposing is the process of finding new uses for previously used items. By extending the usable lifespan of trash and cutting down on garbage creation, reuse helps to protect natural habitats and valuable materials.

Not only does recycling help the environment, but it also helps the wallet. A long-term perspective reveals that the high upfront cost of reusable items is more than justified. By keeping the following in mind, one can find ways to recycle our trash:

- When going shopping, bring along some reusable plastic or cotton bags.
- Old clothing and other stuff may be donated to good causes.
- Water and oil may be stored in plastic gallons.
- Make use of pre-owned media such as books, DVDs, and CDs.
- Invest in a battery that can be charged several times.
- Fix broken gadgets and put them back into use.

c. Recycle:

Reusing anything implies giving it a new coat of paint and a new lease on life. Recycling is the practice of reusing materials that have been discarded through treatment and

alteration. It's done when recycling and conserving resources have failed. Recyclable materials include not just paper and cardboard but also glass, metal, demolition waste, and so on.

- Cardboard, toilet roll, wrapping paper, and so on are all made from recycled paper.
- Boxes for storing eggs, shoes, etc. are made from recycled newspapers.

d. Recover:

The vast majority of trash contains elements that may be recycled or used. This procedure is on the mend.

- Recovering methane gas from decaying organic substances is possible.
- If plastic waste remains after being minimized, repurposed, and recycled. It's a useful material for creating power. Bioremediation is the use of living organisms to transform waste into useful goods.

Barriers to Reducing, Reusing, and Recycling

Companies may have trouble implementing a waste minimization, reuse, and recycling strategy despite their best efforts due to internal roadblocks. The following are some of the reasons:

- Lack of action might be attributed to insufficient time, knowledge, or manpower.
- It may not be financially viable to take action due

to the high upfront costs and lengthy payoff time.

- It's possible that management just doesn't know about the tools at their disposal to eliminate or significantly cut down on waste production.
- The management may not understand how to track the amount of garbage produced or how to establish appropriate goals for reduction.
- In certain cases, enhancing product quality and minimizing waste are mutually exclusive goals.
- It's possible that the company doesn't have environmental policies or the backing of the board.
- It's possible that the environmental policy hasn't been turned into actionable goals and objectives.
- Line management may no longer be responsible for waste reduction due to a centralized environmental department.
- If the department generating the garbage is unable or unwilling to pay for the cost of waste treatment, the facilities department may be responsible for doing so.

3.3. Hazardous Waste

Waste that poses a threat to the environment and human health is known as hazardous waste. Liquids, solids, gases, and sludge are all potential kinds of hazardous waste that may be produced from a wide variety of sources, such as industrial production process wastes and batteries.

Radioactive Waste:

Different criteria are used to categorize this hazardous waste compared to other toxic wastes. In contrast to traditional methods of garbage disposal, scientists have taken a novel approach to the problem.

Although radiation is usually the source of radioactive waste, there are exceptions. However, the contamination levels of "radionuclide" waste are always greater than the legal limits imposed by regulatory agencies. The risk to human health increases in proportion to the number of radioactive materials dispersed all through the waste. Also, the degree of danger posed by different radioactive elements varies.

3.3.1. Main Causes of Hazardous Waste

The major sources of these poisonous chemicals are the hazardous products created by modern industrial and technical processes. The situation worsened dramatically as a result of the Industrial Revolution in the late 18th and early 19th centuries.

Nuclear technology has been a major advancement in the last several decades. Several nuclear uses have recently gained traction in several parts of the world. A result of this is a dramatic increase in the environmental damage caused by radioactive waste dumped on Earth. That has led to serious issues in the biosphere of Earth.

3.3.2. Hazardous Waste Types

There are as many methods to categorize hazardous waste as there are to define what counts as such garbage.

Characteristics:

Certain properties of wastes might make them eligible for "hazardous" labeling:

1. **Reactivity**

Under some circumstances, this kind of garbage causes chemical reactions. This may result in explosions or the release of various gases and vapors. Compression or the addition of water triggers the reaction. Lithium-sulfur batteries and unfired munitions are two such instances.

There is currently no way to determine whether or not a waste is reactive. However, there are other ways to check for this quality, depending on standards for dangerous waste.

2. **Corrosivity**

Many different types of solids, liquids, and gases may be corrosive because they are acids, and bases, or create acidic or alkaline solutions, respectively. Toxic waste is defined as any material having a pH value of 2.0 or above, or below 12.5.

Corrosive liquid wastes are those that can eat away at metal containers such as buckets, storage facilities, and

drums. Used battery acid is one such example. The EPA uses several tests to determine whether or not garbage is corrosive.

3. Ignitability

These wastes may explode, catch fire, or have a flash point below 60 degrees Celsius (140 degrees Fahrenheit) depending on the conditions (spontaneous combustion). Used solvents, as well as waste oil, are two examples of this.

The ignitability of trash may be determined using many tests. The Environmental Protection Agency (EPA) of the United States is one example of a testing regime among many others.

4. Toxicity

Absorption or ingestion of toxic waste may be very harmful, if not fatal. This includes a wide variety of toxins such as mercury, lead, dichlorodiphenyltrichloroethane (DDT), etc. Pollution of groundwater is a potential result of the improper disposal of hazardous waste.

Toxic substances are those that exhibit one or more of the following characteristics:

- **Acute Dermal Toxicity**

This is a skin test for determining if a chemical is mildly poisonous or contains a mildly harmful substance. Some degree of skin toxicity is involved.

- **Carcinogenicity**

The garbage in this case includes a carcinogen in sufficient quantities to warrant special attention. According to World Health Organization (WHO), cancer is one of the leading causes of mortality worldwide.

- **Waste Extraction Test**

Total digestion is connected to the Waste Extraction Test (WET). The results of each laboratory analysis are compared with the numerous hazardous waste rules to establish whether or not the chemical meets the criteria for that designation.

- **Toxicity Characteristic Leaching Procedure**

The Environmental Protection Agency (EPA) defines hazardous waste as wastes that potentially release harmful compounds into the environment, and the Toxicity Characteristic Leaching Procedure (TCLP) is connected to this classification.

The TELP findings are compared to the hazardous waste rules and regulations. Anything not covered by the Resource Conservation and Recovery Act (RCRA) of the Environmental Protection Agency is excluded.

- **Acute Oral Toxicity**

Mildly toxic compounds or those that become mildly harmful when ingested are to blame for this form of

hazardous waste. If waste is harmful when ingested by mouth, we call it toxic.

- **Acute Aquatic Toxicity**

Fish poisoning is linked to the toxicity of waste. To find out whether the waste is harmful enough to aquatic life, it is put through a series of tests.

3.3.3. Listed Wastes

Based on these lists, we know exactly what kind of waste qualifies as harmful. Among the many methods to classify waste are:

1. **Source-Specific**

Chemicals and byproducts from the pesticide and petroleum industries are among those included here. Sewage and sludge from manufacturing and treatment procedures are two further examples of such hazardous wastes.

2. **Non-Specific**

Cleansing and degreasing solvents are only one example of the many industrial procedures included on this list. There are many different types of businesses that use the procedures that generate these wastes.

These pollutants, therefore, come from a wide variety of origins and cannot be traced back to a single origin. The

wastes come from a wide variety of different industrial processes.

3. **Mercury-Containing Products**

These are some wastes containing mercury, particularly mercury devices, fluorescent lights, and goods that hold such switches. They're tied to the problem of what constitutes hazardous waste.

There are many advantages that consumers might get from using mercury-containing items. However, the items become garbage once they are thrown away.

4. **Commercial Chemical Products**

Chemicals that haven't been utilized but will be thrown away fall into this category. Commercial insecticides, industrial chemicals, and pharmaceuticals are some examples. When these chemical compounds are discarded, they constitute a potentially dangerous waste.

3.3.4. Hazardous Waste Management System

1. **Generation**

The Resource Conservation and Recovery Act (RCRA) of the EPA establishes hazardous waste producers as the entry point of the waste management chain. The first step for those who produce garbage is to find out whether and to what extent their trash poses a threat to the environment and society.

One further thing that generators want to do is make sure and prove that the hazardous waste they're producing is actually:

- Identifying
- Maintained
- Treatment

It is essential to follow these procedures before any kind of disposal or recycling.

Each generator's level of EPA oversight is proportional to the quantity of waste it produces. The EPA lists all the rules that must be followed by anyone that produces hazardous waste.

2. Transportation

In the wake of its creation by waste producers, hazardous waste may be moved by transporters to a facility designed to process, dispose of, or recycle the material. Since the garbage is transported over roads, trains, and waterways, it falls within the purview of the Environmental Protection Agency (EPA).

3. Treatment and Storage

The Environmental Protection Agency (EPA) has worked to develop national standards for hazardous waste that can safeguard human health and the planet's ecosystem while also preserving its natural resources. For this reason, there are a variety of methods available, such as recycling

or sending waste to an incinerator or landfill for proper disposal.

Businesses that generate, handle, or dispose of hazardous waste must comply with the regulations established by the Resource Conservation and Recovery Act (RCRA). Facilities that handle hazardous waste in any capacity are required by the Resource Conservation and Recovery Act (RCRA) to get a permit. The collection, documentation, and disposal of trash must adhere to strict regulations.

4. **Disposal**

Traditional landfills have long been used for the disposal of hazardous materials. However, several poisonous substances leaked into the ground as a consequence of this. Over time, the garbage began poisoning the subsurface water supply.

Several modern landfills use protective measures to avoid polluting underground water supplies. An example of a barrier is a fence set up around the base of the dump. Toxic compounds that could otherwise remain in landfill garbage are contained by this.

TSDFs

TSDFs process and dispose of hazardous wastes as well as store them for the short term. The risk might be increased owing to the massive amounts of trash and operations carried out at such sites.

As a result of this problem, TSDFs are subject to stringent rules and regulations. Indeed, TSDF rules are in place for things like:

- Protocols for building administration
- Specifications for Facilities Handling Toxic Waste
- Additional measures for the safety of the earth, its water, and its atmosphere

5. Recycling

There are several advantages to recycling hazardous waste, such as cutting down on the amount of trash that has to be processed and dumped.

It is vital to guarantee the correct storage of the supplies. As a result, accidents like leakage, spillage, fire, and soil and water pollution may be avoided. The Environmental Protection Agency (EPA) has established formal laws to guarantee the integrity of the recycling process.

3.4. Radioactive Waste

There is a special kind of hazardous waste known as radioactive waste because of the radioactive elements it contains. Numerous industries produce radioactive waste, including nuclear medicine, research, power production, rare-earth mining, and the reprocessing of nuclear weapons. To ensure the safety of citizens and the environment, authorities strictly control the final resting places of radioactive waste.

In other words, the nuclear fuel chain is not the only source of radioactive waste. Medical, scientific, industrial, and academic, NDT, and mining applications all rely heavily on radioactive materials. When compared to other potentially dangerous industrial products, radioactive waste poses less of a threat over time since its radioactivity decreases.

3.4.1. Types of radioactive waste

One may consider anything that is naturally or artificially radioactive, or that has been polluted by radioactivity and serves no useful use, to be a radioactive waste.

The half-life of a radioactive substance is the amount of time it takes for 50% of its particles to decay. It is simpler to work with long-lived radionuclides because they release less penetrating alpha and beta radiation than shorter-lived radionuclides, which generate more powerful gamma rays. All radioactive waste eventually disintegrates into non-radioactive substances. An isotope's rate of decay increases in direct proportion to its radioactivity. According to its radioactivity, radioactive waste is often categorized as either low-level waste (LLW), intermediate-level waste (ILW), or high-level waste (HLW).

1. **Low-level waste low**

There should be no more than 4 GBq/t of alpha activity as well as 12 GBq/t of beta-gamma activity in a ton of LLW. Low-level radioactive waste (LLW) may be safely

transported and disposed of without the need for shielding. In addition to the nuclear fuel cycle, other sources of LLW include hospitals and industries. It consists of items like paper, rags, tools, clothes, filters, etc. that have trace quantities of radiation but aren't dangerous for humans to be around for long. Before being disposed of, LLW is often compressed or burned to minimize its bulk. Nearly 90% of all nuclear waste is made up of LLW, yet it only contains around 1% of the radiation.

2. **Intermediate-level waste**

However, the heat generated by ILW (2 kW/m3) is insufficient to be considered into consideration in the design as well as the selection of disposal and storage facilities, even though it is more hazardous than LLW. Shielding is necessary because of the increased radioactivity of ILW. Resins, chemical sludge, and metallic fuel cladding are common examples of ILW, along with contaminated materials after reactor decommissioning. Solidifying smaller things and non-solids in cement or bitumen makes them easier to dispose of. It accounts for around 4% of the radiation and 7% of the quantity of all nuclear waste.

3. **High-level waste**

Due to the high radioactivity of HLW (more than 2 kW/m^3), the temperature of the waste and its surroundings will rise dramatically as a result of the decay heat. This means that HLW has to be cooled and shielded. In a

nuclear reactor, uranium fuel is essentially "burned," and this process produces high-level waste. The transuranic elements and fission products created in the reaction chamber are found in HLW. Only 3% of the trash generated is HLW, yet it contains 95% radioactive. HLW may be broken down into two categories:

- Formerly usable fuel that is now considered garbage.
- The discrepancy between waste and spent fuel recycling was eliminated.

Based on how long it takes for the radiation of certain radionuclides to fall to levels that are regarded as non-hazardous for humans and the environment, HLW may be broken down into long-lived and short-lived elements. If fission products, which have shorter half-lives than actinides, can be isolated from the latter, this separation will have implications for HLW management and disposal. Concerning nuclear power, a lot of attention is paid to HLW, and it is handled properly.

4. Very low-level waste

Very low-level radioactive waste (VLLW) and exempt waste contain radioactive elements below safe exposure levels. Recyclables come mostly from the demolition of nuclear industrial facilities and include things like cement, plaster, brickwork, metals, switches, pipes, etc. Because of the high levels of natural radioactivity in several minerals utilized in other sectors, such as food processing, chemical,

steel, etc., they too generate VLLW in the course of their production. As a result, the trash is thrown out with regular garbage, although some nations are working on VLLW disposal sites.

3.5. Solid, Hazardous, and Radioactive Waste Law and Regulations

3.5.1. Hazardous Wastes Management Regulations

Any material that poses an immediate or potential risk to human health or the environment due to its physical, chemical, reacting, poisonous, combustible, explosion, or corrosive properties is considered hazardous waste.

Managing hazardous waste is addressed by many laws, some of which are more specific than others. Factories Act of 1948; Public Liability Insurance Act of 1991; National Environment Tribunal Act of 1995; Environmental Act regulations and notices. Below, there are a few of the regulations that govern the handling of potentially dangerous waste:

- The Hazardous Wastes (Management, Handling, and Transboundary) Rules, 2008 provided a framework for the control of hazardous wastes and the handling of hazardous substances throughout their production, storage, and import.
- In a similar vein, the Biomedical Waste (Management and Handling) Rules, 1998 were drafted to govern the safe and lawful handling of

infectious waste throughout its life cycle, from collection to final disposal.

- The purpose of the Municipal Solid Wastes (Management and Handling) Rules, 2000 is to provide a methodical framework for the disposal of municipal solid waste.

The Ministry of Environment, Forest, and Climate Change has drafted the Bio-Medical Waste (Management & Handling) Rules, 2015 (Draft BMW Rules) and the Solid Waste Management Rules, 2015 (Draft SWM Rules) in response to shortcomings and overlap of some categories causing inconvenience in implementing the Biomedical Waste (Management & Handling) Rules, 1998 and the Municipal Solid Wastes (Management & Handling) Rules, 2000.

Both the Biomedical Waste (Management and Handling) Rules, 1998, and the Municipal Solid Waste (Management and Handling) Rules, 2000 will be repealed and replaced by the Draft BMW Rules and the Draft SWM Rules, respectively. Both the Draft BMW Rules and the Draft SWM Rules intend to deal with the disposal of garbage, including its source segregation, transportation of waste, diagnosis, and disposal practices. This will help to reduce the generation of bio-medical waste and ensure that it is disposed of in an environmentally responsible manner.

- The primary goal of the E-Waste (Management and Handling) Rules, 2011 was to decrease the use of

hazardous materials in electronic and electrical equipment by specifying a threshold for the use of dangerous materials and to organize the e-waste produced in the country for ecologically responsible recycling. These rules were notified on May 1, 2011, and went into effect on May 1, 2012. As specified in the Rules, they apply to anybody engaged in the production, procurement, sale, or processing of electronic and electrical equipment or components.

- Lead acid battery waste is addressed in detail under the Batteries (Management & Handling) Rules, 2001. The Act mandates that all parties involved in the production, processing, sale, purchase, and use of batteries or components thereof adhere to the provisions of the Batteries (Management & Handling) Rules, 2001. This includes producers, assemblers, reconditioners, distributors, suppliers, brokers, bulk consumers, and customers.

1. **The Environmental Protection Act**

The purpose of this Act, which dates back to 1986, is to set up an adequate safety net. The Federal Government's ability to control garbage of any kind is bolstered by this law. The law is crucial for preventing pollution and controlling trash accumulation. The following are some of the most crucial parts of this Act:

i. According to Section 7 of this Act, it is illegal for any person to release or release environmental contaminants exceeding the set criteria in the course of carrying out any activity.
ii. According to Section 9 of the Act, whenever anything happens that causes damage to the environment, whether such damage is predicted or not, the individual responsible for the damage must take steps to avoid or mitigate the pollutant, released as a consequence of the occurrence. The individual must also report the incident to the relevant authorities in case it causes environmental damage.

The "Polluter Pays Principle" is enshrined in Section 9 (3) of the Act, which declares that whoever causes damage to an area must also pay to restore it to its original condition. We cannot overemphasize the significance of the idea that punishment is meant to be ongoing.

i. The veil of incorporation is pierced by the Act as well. Any director, manager, secretary, or other officials of a firm who knew about or approved of environmental violations committed by that company will be held personally accountable for such violations.
ii. The government established the Environmental Protection Rules, often referred to as the Environmental Protection Rules, 1986, using the authority granted to it by the Environmental

Protection Act. The government may provide particular directives via these channels without revising the underlying Act.

2. **The Hazardous Wastes (Management, Handling, and Transboundary Movement) Rules, 2008**

Hazardous waste management is a difficult problem to solve. It's not optional to adhere to the rules and regulations that make up the legal framework. The Rules impose a duty on the occupant of a hazardous building to ensure the proper disposal of environmental waste. Occupant refers to the person in control of a facility, unit, or industry that generates hazardous chemicals as a by-product of its operations. The occupant is responsible for selling or transporting the hazardous materials to something like a re-processor or recycling that has been granted permission by the government to safely dispose of the trash. The State Pollution Board's approval is also required for any activity involving the accumulation, accumulation, collecting, demolition, converting, reprocessing, etc.

Any business that recycles, reuses or reprocesses garbage is allowed to keep it on its premises for up to three months. If you want to sell or give away any hazardous material, you need to get a registration form from the Central Pollution Control Board beforehand (CPCB). It is also necessary to get a certification from the CPCB before using waste as fuel.

India is a signatory to the Basel Convention, which governs the international transportation of hazardous waste. Although hazardous waste imports for disposal are illegal in India, imports for reuse, energy recovery and recycling are permitted under specific limits. Although hazardous waste exports are permitted in India, they are subject to the approval of the receiving nation.

3. **The Plastic Waste (Management and Handling) Rules, 2011**

The PWM Rules are a code of conduct established to regulate the production, use, and disposal of plastic waste. Everything made of plastic that has been thrown away after being used or having reached the end of its useful lifespan is considered plastic trash. No one other than distributors, consumers, sellers, and makers of plastic items is exempt from the Rule's stipulations. Each plastics producer and recycler must register with the State Pollution Control Board under Rule 9. Every three years, you'll need to renew your registration. No business is allowed to give out plastic bags under Rule 10. Doing so encourages responsible plastic bag use. Details of plastic goods, such as their thickness, color, and plastic classification (compostable, recyclable, or virgin plastic), are also spelled down in the PWM regulations.

The technique for recycling plastic items has been standardized by the Bureau of Indian Standard Specification.

4. **Bio-Medical Waste (Management and Handling) Rules, 1998**

The purpose of these regulations is to guarantee the secure disposal of biomedical waste. Any material left over after performing medical procedures on humans or animals, administering vaccinations, or conducting scientific experiments is considered biomedical waste. Various types of biological waste, including microbiology and biotechnology, human anatomical, animal anatomy, abandoned pharmaceuticals, chemical-related waste, etc., are distinguished in Schedule I of the Rules.

A wide range of facilities, including hospitals, clinics, blood banks, pharmacies, pathology labs, and veterinary clinics, are covered by the BMW Rules. According to the BMW Rules, non-biological wastes must not be combined with any biological wastes. The standard guideline is that within 48 hours, biomedical wastes must be handled or disposed of. According to paragraph one of rule 8, all businesses and institutions that handle biological waste must get a permit from the State Pollution Control Board. The second part of Rule 5 stipulates that all institutions subject to the guidelines must install sterilization equipment such as microwave systems, autoclaves, etc.

5. **The E-Waste (Management and Handling) Rules, 2011**

The primary objective of the EWM is to institute a system that handles e-waste in an environmentally sustainable

manner via the regulation of the problem of disposal and recycling of e-waste. The proper disposal of electronic trash is a serious challenge in India. India is quickly becoming a major player in the Information Technology industry because of its expanding economy and rapidly developing infrastructure. This results in a substantial quantity of electronic garbage that must be disposed of. The situation is exacerbated by a large amount of e-waste that is illegally smuggled into India. Production and consumption are both subject to the E-waste Rules. Bear in mind that some buy electronics in large quantities. There are many large corporations out there that have gone electronic and automated their operations.

Under Rule 3 (k), "e-waste" refers to any electrical or electronic device that has been abandoned or no longer serves its intended purpose. During production, by-products are also considered waste. Rule 4 mandates that the State Pollution Control Board approve all electronic and electrical product manufacturers. The e-waste rules further specify the roles of collecting facilities, end users, wholesalers, and processors.

6. **The Batteries (Management and Handling) Rules, 2001**

A system for the dumping of lead-acid batteries was initiated after notification of the Batteries Rules. The Rules are binding on all producers, recyclers, dealers, importers, assemblers, bulk customers (including organizations and

departments buying more than 100 batteries), and consumers. Under Rule 10, it is the consumer's responsibility to return the spent batteries to the original point of purchase, the manufacturer, or a designated recycling facility. The State Pollution Control Board also requires bulk users to report their use every six months. To import old batteries into India for recycling purposes, a recycler must first secure customs clearance, as per Rule 6. Battery imports will also need proof of registration with the Reserve Bank of India and the Ministry of Environment and Forests, as well as an assurance in the approved format and a copy of the most recent half-yearly report.

3.6. Types of health issues

The degradation of the earth's ecosystems, atmosphere, and water by modernization and development is a major downside. As the world's population and need for necessities increase, so does the quantity of garbage each family throws out every day. Eventually, all of this garbage is dumped into municipal waste collection facilities, from whence it is hauled by local governments and dumped in landfills and dumps. The majority of this waste, however, makes it to its ultimate dumpsites because of a lack of resources or inadequate infrastructure. Any mistakes in this phase of management and disposal may have far-reaching consequences for human health and the environment.

Poor waste management poses a significant threat to public health, particularly concerning the disposal of human excreta and other forms of solid and liquid garbage generated by homes and businesses in the neighborhood. Disease-carrying insects and rodents are drawn to the garbage that has been left out for too long. The smelly decomposition often comes from damp garbage. This results in dirty environments, which in turn increases the prevalence of health issues. Therefore, preventative actions should be taken to reduce the amount of solid waste produced.

3.6.1. Impacts of solid waste on health

The population in places without an appropriate waste disposal procedure, notably preschool children, garbage employees, and personnel in facilities manufacturing dangerous and infectious material are all at risk from the improper disposal of solid waste. Those who live near a landfill or whose water system has been tainted as a result of garbage dumping or leaks from landfill sites are also at increased risk. Injury and illness rates are also known to rise in areas where garbage is allowed to accumulate.

In particular, organic household waste is dangerous because its fermentation generates an environment that is good for the survival and proliferation of microbial infections. Waste collectors and rag pickers are particularly at risk for contracting chronic and infectious illnesses due to their close contact with garbage.

Children are especially susceptible to the negative health effects of being exposed to toxic waste. Diseases caused by chemical exposure may result from direct contact, and chemical poisoning is caused when chemical waste is released into the environment. Over the years, scientists all over the globe have conducted a variety of research to determine whether or not exposure to hazardous waste poses any health risks.

Toxic substances may also be found in agricultural and industrial waste. Furthermore, individuals may be put at risk of exposure to chemicals and radiation through the co-disposal of hazardous industrial waste and municipal garbage. Additionally, stagnate water bodies that provide a breeding ground for illness may grow when solid waste is not removed. Water bodies and groundwater may be tainted when waste is placed close to them. The buildup of harmful compounds in the food supply chain through the animals and plants that depend on it is a direct outcome of the direct disposal of unprocessed trash in rivers, oceans, and lakes.

Since it poses serious health risks, proper care must be taken when disposing of medical waste from hospitals and other medical facilities. Thrown-away syringes needles, gauze, wipes, plasters, and other infectious debris are often disposed of with ordinary garbage at hospitals, clinics, labs, and research facilities.

Neighborhoods near landfills and other waste processing

facilities are also vulnerable to contamination and other health risks. Air pollution results from poorly managed incinerators and disease-carrying insects and rats are attracted to landfills that lack sufficient management and construction. These locations need to be as far away from any human habitation as possible. To prevent contamination of adjacent water supplies, landfills must be completely enclosed and sealed.

If safety measures are not performed, recycling might pose threats to people's health as well. When dealing with chemical and metal waste, workers run the risk of being exposed to harmful substances. Discarded syringes, for example, pose a significant risk of transmitting diseases like hepatitis C and hepatitis B to anybody who handles them. People who rummage through trash heaps in search of recyclables are at risk of becoming hurt and coming into touch with these pathogens.

3.6.2. Diseases from Solid waste

Untreated releases of chemicals including toxic elements, mercury, as well as polychlorinated biphenyls pose serious health risks to humans. Cancer rates are much higher in populations who have been exposed to hazardous waste, according to certain research. Over the years, scientists all over the globe have conducted a variety of research to determine whether or not exposure to hazardous waste poses any health risks.

3.6.3. Occupational hazards associated with waste handling

1. **Infections**
    - Illnesses of the skin and blood are caused by coming into touch with garbage or having open wounds.
    - Exposure to contaminated dust, most often during landfill operations, may cause eye and respiratory diseases.
    - The bites from animals who have been feasting on the garbage may spread a variety of illnesses.
    - Flies that feed on garbage may spread intestinal illnesses.

2. **Chronic diseases**
    - Dust exposure and toxic substances pose a risk of chronic breathing problems, including cancer, for workers in the incineration industry.

3. **Accidents**
    - Bone and muscle problems from constantly lifting and carrying heavy containers.
    - Cuts and puncture wounds are more susceptible to infection.
    - Poisoning as well as chemical burns may occur even when just a little quantity of

dangerous substances waste is present in the overall garbage.

- Injuries, including burns, are sustained by workers in landfills or methane gas explosions at landfills.

3.6.4. Preventive measures against solid waste

Waste must be disposed of appropriately to prevent damage to local ecosystems and health problems for residents.

The ideal way to dispose of organic waste is by composting, which may be done at the home level if adequate waste segregation is practiced. The waste's organic component quickly rots away, draws bugs, and spreads illness. Composting organic waste becomes a useful fertilizer.

Chapter 4

Air Pollution

4.1. Meteorology and Air Pollution

Short-term changes in the atmosphere and their subsequent effects on Earth are the focus of meteorology. Meteorology, or the study of weather, is the study of past, present, and perhaps future conditions in the atmosphere. Temperatures, humidity, precipitation, wind, barometric pressure, and weather patterns are all aspects of the weather that help paint a picture of the current conditions in the sky.

The path that air pollutants take is affected by wind patterns. As a result, an analysis of air pollution has to include a review of the regional climate. Pollutant concentrations increase when winds die down and airborne particles have nowhere to go. Pollutants, on the contrary hand, are more easily dispersed when high, turbulent winds are blowing.

The weather forecast is useful since it:

- Climate models may be used to foretell air

pollution occurrences such as variants and days with high pollution concentrations
- Discover exactly where the pollution is coming from
- Modeling techniques may be used to simulate and forecast air quality.

The following variables are useful for measuring air quality and providing insight into atmospheric chemical changes:

- Wind Speed And Direction
- Temperature
- Humidity
- Rainfall
- Solar Radiation.

- **Wind speed and direction**

Recordings of wind speed data may help pinpoint the guideline and location of pollutants when a monitoring system detects an increase in pollution concentrations. To improve air quality, it is necessary to first identify the causes of the problem.

A device called an anemometer is used to calculate wind velocity. The sonic accelerometer is used at our monitoring sites.

The premise behind a sonic measurement device is the relationship between wind speed and the duration it takes for sounds to travel through the air. It's faster for sound to

move with the wind than against it. Sonic anemometers can estimate both wind velocity and direction by observing the velocity of sound waves in two directions simultaneously.

- **Temperature**

Taking temperature readings helps in assessing, modeling, and forecasting air quality. Photochemical smog is formed from various air pollutants by a series of chemical processes in the atmosphere, which are greatly influenced by temperature and solar radiation. To a greater extent, smog may be produced when circumstances are favorable.

Platinum wire, whose resistance fluctuates with temperature, is often used as a temperature measurement standard. It's measured by a sensor, which then provides an accurate temperature measurement.

- **Humidity**

Atmospheric water vapor is a key component in so many thermal as well as photochemical processes, alongside temperature and sun radiation. Water's small size and its high polarity allow it to form strong connections with many different substances. When coupled to airborne particles, their ability to disperse light is greatly enhanced. Erosive gases, like sulphur dioxide, may be dissolved in water and turn into an acidic medium that is harmful to both people and property.

The amount of water vapor in the air is expressed as a

proportion of the water vapors pressure at saturation at a specific temperature. That percentage represents the relative humidity in the air. When considering factors such as location, proximity to water bodies, wind direction, and air temperature, it is clear that the quantity of water vapor in the atmosphere varies greatly.

The polymer film's absorbance characteristics are used to provide an accurate humidity reading. As the humidity of the air around it fluctuates, the film either takes in or gives out water vapors. A sensor monitors the environment for these variations and provides a measurement of the relative humidity in the space.

- **Rainfall**

Smog is cleaned up by rain because it washes away particles and disperses gaseous contaminants. Clarity is enhanced when the dust is swept away. High-precipitation areas tend to have cleaner air. The formation of acid rain may cause harm to materials and plants if rainwater mixes with gaseous contaminants like sulphur dioxide.

Whenever the rainwater has flowed from the funnels into the upper compartment, the bucket will tilt in the other direction, bringing the rain-filled compartment to rest against the stopper on the opposite side of the bucket. When one chamber is full, the water in the other begins to fill up.

Using the funnel's size, the frequency of bucket

movements, and the pace at which they occur, the device determines the rainfall's total volume and intensity.

- **Solar radiation**

Considering that the intensity of the sunlight has a significant impact on the pace of the chemical processes that cause smog, monitoring solar radiation is crucial for use in modeling photochemical smog occurrences. Sky conditions, time of day, and latitude all have a role in how much sunlight reaches the ground.

The measurement device is a device used to calculate solar radiation using readings from silicon cell sensors.

4.2. Measurement of Air Quality

Measuring air pollution entails taking samples of polluted air and analyzing them for several factors, including the concentrations of various gases and the sizes of various particles. Simple smoke and dust collectors called deposit gauges as well as rain gauges used in acid rain investigations date back to the early days of pollution monitoring. In the present day, there are a wide variety of instruments and methods that may be used automatically and accurately to assess air pollution. On one extreme are the diffusion tubes, which are simple absorbent scientific processes, and on the other are the very complex physical and chemical detectors that provide almost real-time measurements of pollution and are utilized to build air quality indexes.

4.2.1. Importance of measurement

There are several contributors to poor air quality. Many different gases and solids and liquids particles such as soot from vehicles and fly ash from incinerators may be found in urban air most commonly sulphur dioxide, nitrogen oxides, and carbon monoxide, all related to fuel combustion. The consequences of these many types of pollution on human health, and the environment including groundwater, soils, plants, trees, and other plants, and man-made structures vary widely. To maintain air quality within legal limits required by authorities like Environmental Protection Agencies or advisory standards proposed by agencies like the World Health Organization (WHO), monitoring pollution levels is the first step.

4.2.2. Passive and active measurement

Air pollution may be quantified in main methods: passive and active.

Passive measurement

In contrast to active gadgets, passive ones are easy to make and cheap to buy. They function by absorbing or passively collecting samples of the surrounding air, which must then be tested in a laboratory. Diffusion tubes, which resemble test tubes and are attached to things like lamp posts to absorb one or more particular pollutant gases of interest, are a typical kind of passive monitoring. The tube is removed after a certain amount of time and submitted to a

lab for analysis. Similarly, deposition gauges, one of the first methods of pollution monitoring, are also passive instruments. The enormous funnels, which may be used to collect soot and other particles, then funnel the collected material into sample bottles for later laboratory analysis.

Active measurement

While more accurate and dependable, active measuring equipment is more mechanized, complicated, and advanced. Ventilations are used to draw in the air, which is then filtered and either instantly analyzed at the scene or collected and stored for later laboratory study. Both chemical and physical processes may be used in active sensors. Using a certain light wavelength, for instance, a physical approach measures the amount of air in a sample without altering the material in any way. The sample is subjected to a chemical process, and the resulting change is then quantified. Active measuring is used by most automatic air quality sensors.

4.2.3. Methods of measurement for different pollutants

Two gases, nitrogen, and oxygen, both are crucial to life on Earth and make up the vast majority of the air we breathe. But there are numerous other gases and molecules, too, although at much lower concentrations. With the use of the AQI, we can keep tabs on five of the most prevalent air pollutants:

- Ozone at the surface
- Hazardous concentrations of carbon monoxide
- Carbon disulfide
- Substances containing nitrogen dioxide
- Particles in the air are sometimes called aerosols.

Ozone at ground level as well as particles in the air is the two most dangerous types of air pollution. These are also the primary causes of smog, a kind of air pollution that limits one's ability to see far ahead.

There is a need for specialized methods, instruments, and chemical reactions to quantify the many sources of air pollution. Gas chromatography, several types of spectrometers, spectroscopic, spectrometric, and flame photometry are all examples of analytical chemistry methods used to quantify environmental contamination.

1. Particulates

Until the latter part of the twentieth century, it was common practice to visibly and somewhat crudely estimate the quantity of soot created by a structure like a chimney by holding cards up with lines drawn onto them to signify various shades of grey. These days, a tapered element oscillating microbalance (TEOM) based on a glass container that vibrates less or more as collected particles pile on it is used in pollution monitoring stations to provide accurate readings of both coarse (PM10) and tiny (PM2.5) particulates. Other types of particulate matter samplers, such as optical photodetectors, which assess the

amount of light reflected by samples of light larger particles reflect more light, and specific gravity analysis, which involves collecting samples of light through filters and weighing them, can also be used to measure particulates.

2. Nitrogen dioxide

Diffusion tubes allow for the passive measurement of nitrogen dioxide; however, the collection, analysis, and reporting of data takes some time. A fluorescent dyes analyses, which analyzes nitrogen oxide concentrations from the lights they emit, is another active method that yields significantly faster results. Throughout the United Kingdom, NO2 is tracked in real-time at over 200 locations using fluorescent dye sensors.

3. Sulphur dioxide and hydrogen sulphide

SO_2 may also be measured using the absorption spectro-photometric method. To determine the concentration of various sulphur compounds present in the air, flame photometric detectors are used.

4. Carbon monoxide and carbon dioxide

Non-dispersive infrared (NDIR) amount of light absorbed based on the Beer-Lambert equation is used to quantify carbon monoxide (CO) as well as carbon dioxide (CO_2). Electrochemical gel detectors, as well as metal-oxide semiconductors (MOS) detectors, are two other methods for CO measurement.

5. **Ozone**

The concentration of ozone (O3) in the air may be determined by analyzing the amount of light contained within a given air sample. According to the studies, higher concentration levels absorb more light.

Natural measurements:

Biomonitoring, which includes the study of how contaminated air affects living organisms, may provide a qualitative assessment of air pollution. Strawberries and other plants produced in controlled environments have been employed in several scientific studies.

4.2.4. Measurement units

Parts per billion (ppb) or parts per million (ppm) or micrograms per cubic meter (g/m3) are often used to represent the concentration of a pollutant in the air. Taking into consideration the varying molecular weights of gases as well as their temperatures and pressures, it is easy to convert between the two systems. A single quantity on an easy-to-understand and commonly color-coded scale are generated by averaging the levels of a "basket" of typical air pollutants such as ozone, carbon monoxide, sulfur dioxide (SO2), nitrogen oxides, as well as fine and coarse particles in urban areas.

4.3. Air Pollution Control

Controlling air pollution entails a variety of strategies aimed at decreasing or preventing the release of pollutants

into the atmosphere. Along with sewage treatment, solid-waste treatment, and hazardous-waste management, air quality control is one of the main areas of pollution control.

Air pollution occurs when harmful compounds are present in the atmosphere for extended periods and at high enough concentrations to produce injury or undesired consequences. Negative consequences on people, their possessions, and the ability to see outside are all on the list. Both natural and human-caused activities may pollute the air we breathe. Volcanic activity and wildfires are two examples of natural occurrences that might have far-reaching global consequences. However, only pollution from human-caused sources, such as industry and traffic, may be reduced or eliminated.

4.3.1. Measures to control air pollution:

To reduce air pollution, one may follow the appropriate steps:

1. **Avoid Using Vehicles**

When possible, pedestrians should travel rather than drive. Instead, they should rely on public transportation wherever possible. This has the added benefit of reducing energy use without sacrificing pollution prevention.

2. **Energy Conservation**

To produce electricity, a substantial quantity of fossil fuels

must be burned. Consequently, be sure to turn off the electronics whenever they are not in use. You may do your part to rescue the planet from a purely individual perspective. To a lesser extent, the use of energy-efficient equipment like CFLs also helps reduce pollution.

3. **Use of Clean Energy Resources**

Solar, wind, and geothermal energy all help cut down on pollution levels in the atmosphere. Many nations, India included, have adopted this practice as a means of cleaning up their ecosystems.

Additional methods for reducing air pollution typically involve:

- By limiting one's consumption of flammable materials.
- Industrial emissions are a significant contributor to air pollution, although the pollution may be mitigated by regulating or treating the emissions at their point of origin. If a certain raw material's reactions produce a pollutant, for instance, then that raw material may be swapped out for one that produces less pollution.
- Changing to a different fuel is yet another strategy for reducing pollution in the air. Vehicles powered by CNG (compressed natural gas) are gradually replacing those that run on gasoline and diesel in various areas of India. The majority of automobiles on the road today use them since their emissions

systems are less than perfect.

- Although India has several traditions aimed at improving air quality, most of them have been lost or are not being implemented correctly. Many cars and trucks are still on the road despite never having passed an emissions test.
- Industry-caused air pollution may also be reduced by upgrading and maintaining existing machinery to reduce emissions.
- Attempts to eliminate pollution at its origins often fail. Then we may use pollution-prevention tools like process control devices.
- Depleting harmful emissions is a highly efficient approach to reducing air pollution.
- The planting of trees is the last and best hope for mitigating the impacts of air pollution. Many airborne contaminants are mitigated by the presence of plants and trees. In a perfect world, tree planting in polluted regions would have a significant impact.

4.4. Air Pollution Law and Regulations

- **The air (prevention and control of pollution) act, 1981**

An Act to create Boards to prevent, control, and abate air pollution, to bestow on and assign to such Boards authorities and responsibilities related thereto, as well as to address issues associated therewith.

Given that decisions were made to preserve the quality of air and control air pollution during the United Nations Conference on the Human Environment held in Stockholm in June 1972, in which India took part.

The purpose of the Air Act of 1981 is to regulate pollutant levels and prevent deterioration of air quality. To improve the air quality and prevent, regulate, or subside air pollution within the country; to provide government advice on any matter related to air quality and air pollution prevention, regulate, or environmental cleanup; to develop and implement a plan for the preventative measures, regulation, or eradication of air pollution; to gather, collate, and publicly release technical as well as data for statistical analysis regarding air pollution and also the measures are taken to combat it; and to retrieve, assemble, and publish data on the effectiveness of those measures.

- **Environment Protection Act, 1986**

In 1986, Congress passed the Environmental Protection Act. The Department of Environment in India has been in place since 1980; hence its repeal was not necessary. This agency rebranded itself in 1985 as the Ministry of Environment and Forests. In a similar vein, in 1981, this measure predated The Air (Prevention and Control of Pollution) Act. The goal of this legislation is to enhance environmental conditions and safeguard people, other animals, plants, and property from potential dangers.

According to the act, "environmental pollution" is characterized by the presence of every environmental hazard, and "environmental pollutant" is defined as any solid, liquid, or gaseous material present in such proportion as may be, or likely to be, damaging to the environment.

No human could relieve or radiate or allow to be dismissed or released into the atmosphere any environmental contaminant in overabundance of such specifications as may be recommended, and no person shall manage or cause to be addressed any harmful chemical expertly in full conformity with such method and after ensuring compliance with such protective measures may be prescribed. That whoever fails to cooperate or contravene shall be subject to imprisonment for a term not to exceed five years or a fine not to exceed one lakh rupees, or perhaps both; and in the case of violation or if the breach of the rules continues, upon conviction for the very first such failings or contravention, shall be liable for additional years or with fine to 5000 rupees for each day and during that such failure or clear violation continues. Finally, a sentence of imprisonment for the duration which may extend to 7 years shall be punished if it persists for further than a year following the date of conviction.

Every director, manager, secretary, or even another officer of the corporation who, at the time the offense has been committed, seemed to be directly in control of and fully accountable to the corporation for the conduct of the

company's operations of the corporation, as well as the company, shall be deemed to be guilty of the offense and is liable to be pursued and punished accordingly if the company is found guilty of any offense committed under this act.

4.5. Noise Pollution and Control

The Latin root "nois" means "to feel the desire to heave," hence the English word "noise" may be traced back to the concept of nausea. Unpleasant noise is the source of much human distress. Decibels are used to quantify how loud something is (dB). A person can detect sounds as low as 1 db. The rising decibel levels in and around human settlements have made noise pollution an issue of national importance. Automobiles, planes, factories, loudspeakers, fireworks, etc., are all big contributors. The TV, the stereo system, the radio, etc. all contribute to noise pollution when played at excessive volumes.

4.5.1. Types of Noise Pollution

The three main categories of pollution are as follows:

- Transport Noise
- Neighborhood Noise
- Industrial Noise

1. Transport Noise

The number of cars on the road has grown throughout the

years, leading to a corresponding rise in traffic noise. Deafness in the elderly, headaches, high blood pressure, and other health problems are all linked to the rise in noise pollution.

2. **Neighborhood Noise**

The commotion is caused by various electronic devices, kitchen appliances, and other sources. Devices, radios, loudspeakers, etc. are major contributors.

3. **Industrial Noise**

This loud noise is produced by large factory machinery. Many studies show that industrial noise pollution causes a 20% decrease in hearing capacity.

4.5.2. Causes and Sources of Noise Pollution

The following are some examples of what produces and contributes to noise pollution:

- Noise pollution has increased as a consequence of industrialization because of the widespread use of noisy gear like generators, mills, and enormous exhaust fans.
- Automobiles the second cause of noise pollution is the ever-increasing traffic volume on the highways.
- The use of loudspeakers to broadcast music at events like weddings and public gatherings might cause disturbances in the surrounding community.
- The noise from mines, construction of buildings,

and other similar activities, among others, contributes to the overall level of ambient noise pollution.

4.5.3. Noise Pollution Examples

Some common types of noise pollution are as follows:

- Excessive use of horns
- The use of public address systems for either religious or political events
- Fireworks are being used needlessly
- Mechanical roar
- Noise from the construction site
- Transmission noise from trains and planes.

4.5.4. Effects of Noise Pollution on Human Health

Some exposure to noise pollution may be harmful to human health:

- Long-term exposure to loud noise pollution raises blood pressure, which has a direct impact on health.
- Hearing loss occurs when the eardrums are repeatedly subjected to noise levels that are much over the audible range for humans.
- Sleep disorders: Not getting enough shut-eye might make you sluggish and irritable throughout the day. Having trouble sleeping due to noise pollution is a certain way to feel irritated and uneasy.
- Heart problems: Even healthy people might have

troubles with their hearts from time to time, such as a spike in their blood pressure, tension, or the onset of a cardiovascular illness.

4.5.5. Prevention of Noise Pollution

Following are some things you can do to lessen the impact of noise pollution:

- Honking should be prohibited in all public buildings, including schools, hospitals, and other such establishments.
- Appropriate soundproofing measures should be put in place in all public buildings, including offices, hospitals, and factories.
- The volume of musical instruments has to be managed so that it doesn't go too much beyond acceptable levels.
- Preventing noise pollution by planting trees densely.
- Wilderness, steep terrain and mining zones are off-limits to anybody carrying explosives.

4.6. Types of health issues

Health Issues from Air Pollution

Polluted air may have negative effects on the health of everyone, regardless of how healthy they already are, including respiratory discomfort or difficulty breathing during exercise or outings. The likelihood of negative

health impacts from breathing polluted air is contingent on several factors, including your existing health, the kind and quantity of the pollutants, and the duration of your contact with them.

Immediate health issues caused by high levels of air pollution include:

- Complications of pre-existing heart and respiratory disease
- Increased demand for oxygen from the lungs and heart results in increased strain on these organs.
- A weakened respiratory system due to damaged tissue

To name just a few of the long-term health implications of breathing contaminated air:

- Lung aging that progresses too quickly
- Capacity reduction and diminished lung function
- Bronchitis, asthma, pneumonia, and even cancer development
- Age-related decline in longevity

Groups of people most at risk for serious health effects from air pollution include:

- Patients suffering from cardiac issues such as coronary heart disease or heart failure
- People who suffer from respiratory illnesses such asthma, COPD, and emphysema (COPD)
- ladies who are expecting a child

- People who labor in the open air
- Persons in their later years and the elders
- Minors younger than 14
- Outdoor athletes that train at high intensity

These types of people may be more sensitive to the negative health consequences of air pollution, or they may experience them at lower exposure levels.

4.6.1. Health Issues from Noise Pollution

Impact on mental health

The consequences of exposure to unwanted noises on mental health are multifaceted. Even while we're fast asleep, our brains are listening for threats in the environment. Therefore, noise, particularly continuous or loud noise, may be a source of tension or worry. A person's susceptibility to stress rises in tandem with their duration of exposure to noise pollution.

Noise pollution may make people irritated, on edge, annoyed, and even furious. Someone's mental health might be negatively affected by noise even more if they believe they have no choice in the matter.

Noise in the environment is a typical contributor to insomnia. As a result, a person could feel:

- Problems falling asleep
- Insomnia, or the inability to fall asleep,
- Awakening Unusually Early

In addition to decreasing the length and quality of sleep, sounds may also affect the percentage of Rapid Eye Movement (REM) time.

Impact on physical health

Noise pollution's physical health impacts might arise from being exposed to the noise either immediately or later.

Loud noises may be the direct cause of permanent hearing loss in certain people. Noise-related hearing loss may take many different forms.

- Impression of abnormally high volumes
- Tinnitus is the medical term for the constant, intense buzzing in the ears caused by tinnitus.
- Hearing loss (paracusis)

It has been hypothesized by some researchers that noise pollution could potentially have a role in aggravating preexisting health problems. Short-term contact with noise pollution has been shown to temporarily elevate blood pressure and blood viscosity, according to a research report in 2018. Heart disease is another health issue linked to chronic noise exposure.

It has been assumed by the review's authors that this is because noise pollution raises cortisol and other stress estrogen levels and disrupts the neurological system. The disease may eventually manifest as a result of this prolonged stress.

Preeclampsia, a disorder characterized by high heart rate during pregnancy, was shown to be more prevalent among pregnant individuals exposed to greater levels of noise pollution, according to research conducted.

Impact on children

Children are more susceptible to noise-induced hearing impairment than the adult. According to research from 2014, it has shown that children's hearing may be permanently altered by being exposed to sound for 8 hours a day, with certain frequencies becoming inaudible.

An expert says that children's hearing might be damaged by noise pollution throughout pregnancy, infancy, and adolescence. Children may also find it difficult to concentrate and learn if they are exposed to excessive or distracting sounds at school or home. As a result, they may have greater trouble with:

- Concentration
- Progress in Verbal and Nonverbal Interaction
- Mental capacity

A child's conduct, social skills, and self-esteem might all be negatively impacted by this. Additionally, prolonged noise exposure might raise blood pressure.

Chapter 5

Environmental Impact and Economic Assessment

5.1. Pollution and Environmental Ethics

What we mean by "environmental ethics" is the study of how human activities and beliefs affect the natural world. Although it gained notoriety between the industrial revolution as well as the 1970s, this school of academics and psychological thinking has been around since before the birth of agriculture.

Without these crucial debates and the appropriate use of both nonrenewable and renewable resources, our Earth which a future generation inherits through us would be uninhabitable. Without concern for the environment, Earth may soon become uninhabitable.

Some of the problems our world is facing include global warming, climate variability, degradation, pollutants, resource depletion, and the risk of extinction. The study of environmental ethics is fundamental to environmental science because it defines humanity's place in the natural

world. When you follow the principles of environmental ethics, you know you're helping to preserve the planet for future generations.

Human activities are the primary cause of environmental degradation. We all have basic needs like food and shelter, and the increased demand for these things further exacerbates the situation. The delicate equilibrium of the ecosystem is disrupted when these products are in such high demand. Technology advancements are leading to the depletion of natural resources and damage to the environment. Numerous environmental problems have wreaked devastation on Earth and its inhabitants. Human survival will be severely limited in the not-too-distant future if these negative repercussions are disregarded now.

Significant environmental concerns include pollution, overpopulation, industrial and residential sewage, acid rain, rising sea levels, ozone depletion, urban expansion, bioengineering, deforestation, and global warming. These environmental problems have already begun to have disastrous effects, such as the impact on human health, rising sea levels, exhaustion of non-renewable sources, melting glaciers, species extinctions polluted landfills, poisonous dust, reducing soil quality, increasing water, and air pollution, and many others.

Pollution and environmental imbalance are the results of industrialization. If a business is to blame for these

difficulties, it is everyone's responsibility, not just the industries. It is these complex issues, which environmentalists group under the umbrella phrase of "environmental ethics," that they are attempting to resolve. Everyone must take responsibility for upholding environmental morals. Altering your behavior to conform to environmental standards might be challenging.

The ethics of the environment and the ethics of business are two areas that need to be examined in today's society. These incidents are increasingly commonplace in today's culture. The use of oil and coal is detrimental to the health of the planet and all living things on it. Both are quite dangerous if consumed in their unprocessed form. Regardless of whether they contribute to the formation of these natural catastrophes, they nonetheless damage the atmosphere, grounds, and waters. Both are temporary and can be done without, so it's best to get rid of them as soon as possible.

5.1.1. Environmental Ethics and Its Principles

Methods and concepts from a variety of fields may help us decide how much weight to give certain aspects of the natural world. Because of the sheer size and breadth of the area, no one guiding concept can hope to include it all. Over the years, several theories have developed, with each one emphasizing a unique set of environmental ethical concepts. Following is a list of all the recurring ideas from those concepts.

1. **Anthropocentrism**

This statement implies that humans are more significant than any other species. Everything else in the world is just a prop to help them make it. The concept of anthropocentrism may now be broken down even further into two subcategories. There are two types of anthropocentrism: weak and powerful.

Weak anthropocentrism, on the other hand, places humans at the center of everything since, according to this theory, only humans can properly understand and hence change their surrounding environments. A strong anthropocentric, on the other hand, would argue that humans should be in the center because they are the most deserving. This was a distinction that Peter Vardy drew.

2. **Non-Anthropocentrism**

This philosophy, in contrast to both anthropocentrism and non-anthropocentrism, recognizes the worth of everything in the natural world, including humans. A belief in this concept is a belief in anything in nature that can maintain its existence.

3. **Psychocentrism**

When compared to other elements of the environment, human beings are seen to be more valuable because their minds are significantly more developed and complicated.

4. **Biocentrism**

It's not just a buzzword without political weight. It's a

worldview that considers every living thing to be of equal worth. Biocentrism is the environmental ethical philosophy that safeguards the planet's ecological stability.

5. **Moral considerability**

This is another crucial tenet of ecological morality. It's the recognition of this inherent worth in all living things that prompt us to act morally. To have moral regard for a creature is to accept that all of our dealings with that person are subject to moral norms.

5.1.2. Types of Environmental Ethics

Numerous environmental ethics had emerged in response to the proliferation of ideas in this area. Some safeguard the human race, while others defend the natural world. Types here include the following:

- The study of how people interact with their surroundings is known as "social ecology."
- All living things should be treated with respect since this is a fundamental tenet of deep ecology.
- The ecofeminism perspective encourages us to see Earth as a woman and treat her with more respect.

5.2. Environmental Risk Analysis

To prevent harm to people or ecosystems from polluted land or water, professionals employ a technique called environmental risk analysis (ERA), often referred to as quantitative risk analysis (QRA).

The goals of an ERA are to give a numerical or qualitative risk estimate and data for evaluating the potential consequences of certain soil pollutants. It is from this analysis that choices on the level of risk tolerance and the necessary precautions for preserving human health and ecological systems may be derived. By using the ERA, you can also find out what safe levels are for each component being tested.

5.2.1. Environmental Risk Analysis methodology

The four stages are as follows: hazard identification; toxicological evaluation; risk assessments; and risk characterization methods.

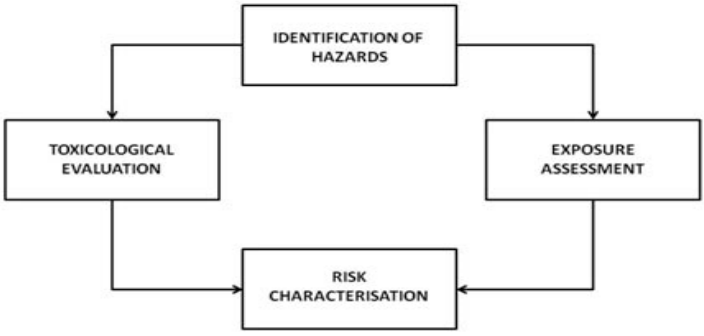

Figure 5.1:- Process of Environmental Risk Analysis[*]

Stage1: Identification of Hazards. The first step is to develop a theoretical design of the location under study, including its contaminated hotspots, chemical compounds,

[*]https://www.emgrisa.es/en/wp-content/uploads/sites/4/methodology-analysis-emgrisa-001.jpg

underground distribution, transport processes, exposure pathways, and possible receptors.

Stage2: Toxicological evaluation. Toxicological assessments are performed to determine how dangerous potentially poisonous chemicals are through:

- Determining whether or not contact with an active ingredient will enhance the negative impacts on health requires identifying the risk.
- The increasingly complex and challenging for a potentially vulnerable population is established by dose-response analysis, which calculates the maximum safe daily consumption.

Stage3: Exposure assessment. The goal is to determine the safe daily intake of chemical agents and their potential targets. This conclusion is based on the identified concentrations of the harmful chemical components and the potential exposure pathways under consideration. One of two different ways chemical substances may enter the body is through:

- When dirt is ingested or comes into direct touch with the skin, exposure occurs. It has been decided that the concentration found in the soil represents the exposure concentration.
- Inhaling volatile chemicals found in soil and groundwater is one kind of indirect exposure. In this instance, direct measurements or transport models may be used to determine the exposure

concentration. Knowing the geology and hydrogeological qualities of the medium, the extent of the exposure route, and the location of the receptors, as well as the nature of the construction and condition of enclosed places like basements, offices, sewers, etc., is essential.

Stage4: Risk characterization. To achieve this, we need to combine data on the toxicity of individual chemical compounds with data on how much of those chemicals' potential receptors were exposed at a given dosage. The data is sent into software that calculates the precise level of danger present at the location in question. With a risk's output being an estimate, defining the degree of uncertainty is crucial.

The following is taken as given in terms of human health protection after an Environmental Risk Analysis (ERA) or Quantitative Risk Analysis (QRA):

- When it comes to toxins, one per one hundred thousand incidences of cancers in exposed individuals is considered an acceptable risk. no more than a risk value of 10-5
- In the case of chemicals with systemic effects, the condition of acceptable risk is deemed to exist if the quotient of the maximum allowable dosage by the product of the long-term exposure is less than one for each substance.

Procedures to remove or decrease to acceptable

concentration levels for potentially vulnerable receptors must be implemented if the QRA reveals an unacceptable risk.

When cleaning up a polluted area, the ERA can help determine whether quantities of chemicals are safe enough that they won't harm any nearby organisms. That is, the Site Specific Target Level (SSTL) is for the origin site.

5.3. Elements and Atomic Weights

A chemical element's atomic weight is the proportion of the average atomic mass of that factor to standards. One-twelfth of the weight of a carbon-12 atom has been used as the standard atomic mass unit since 1961. There are several species of atoms that make up a given chemical element, and each of them has a bit distinct atomic mass number (the sum of the atomic number of protons and neutrons). On average, the proportion of natural abundance and diversity of helium's isotopes yields an atomic weight of 4.002602 for the element as a whole. The atomic mass unit (amu) is written as a dalton, and is the unit of measure for atomic weight.

Due to the prevalence of simple numerical correlations among atoms in chemical processes, the notion of atomic mass is central to the study of chemistry. It is almost hard for chemists to directly count the atoms involved, thus they instead use weight to quantify reactants and products and use atomic weight estimates to conclude. The leading scientists of the late nineteenth and early twentieth century

were preoccupied with this issue. Their meticulous laboratory work ultimately proved vital to the advancement of chemical research and technology.

When chemical products are purchased and sold based on the presence of one or even more specified components, accurate measurements for atomic mass serve a crucial role in a very different manner. Examples include the chemical manufacturing of soda ash and the ores of rare metals like chromium and tantalum. Quantitative analysis is required to ascertain the amount of the required component. The value that is calculated for the material is affected by the atomic weights that are used.

Atomic Masses

	1A	2A											3A	4A	5A	6A	7A	8A
	(1)	(2)											(13)	(14)	(15)	(16)	(17)	(18)
			3B		4B	5B	6B	7B	—	8B	—	1B	2B					
			(3)		(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)					
1	H																	He
2	Li	Be												B	C	N	O	F	Ne
3	Na	Mg												Al	Si	P	S	Cl	Ar
4	K	Ca	Sc		Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
5	Rb	Sr	Y		Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
6	Cs	Ba	La		Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
7	Fr	Ra	Ac		Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Uub	—	Uuq	—	—	—	—
6					Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu	
7					Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr	

Atomic mass, expressed in terms of the atomic mass unit, is the average mass of an element's atoms (amu, also known as daltons, D). The atomic mass is generally calculated by multiplying the weight of each isotope of an element by its abundance to get an overall average.

Experiments have shown that neon includes three isotopes, each with a different number of neutrons and protons in its nucleus: neon-20 (including 10 protons as well as 10 neutrons inside its nucleus) has a volume of 19.992amu as well as an abundance of 90.48%; neon-21 (including 10 protons as well as 11 neutrons inside its nucleus) has a volume of 20.994amu as well as an abundance of 0.27%; and neon-22 (with In this way, we may calculate neon's mean atomic weight:

0.9048 ×	19.992 amu	=	18.09 amu
0.0027 ×	20.994 amu	=	0.057 amu
0.0925 ×	21.991 amu	=	2.03 amu
			20.18 amu

When combined with the mole idea, the atomic mass becomes beneficial in chemistry; one mole of any given element has the same mass in grams as its atomic mass, measured in amu. A mass of iron atoms might weigh 55.847 grams, given their atomic mass is 55.847amu. In the same way, the same idea may be applied to molecules and ionic compounds. A mole of sodium chloride (NaCl) would weigh 58.44 grams, with one formula unit weighing

58.44amu (22.98977amu for Na + 35.453amu for Cl). One water molecule (H_2O) weighs 18.02amu (21.00797amu for H + 15.9994amu for O), while a mole of water molecules has a mass of 18.02 grams.

5.4. Physical Constants

Physical constants are quantities in physics that are thought to be both universal and unchanging across time; they are sometimes called basic physical constants or universal constants. It stands in contrast to a mathematical constant, which has a fixed numeric value but is not determined by any kind of physical measurement.

The light's speed in a vacuum c, the acceleration of gravity **G**, the Planck variable **h**, the electric constant **0,** and the elementary charge **e** are only a few of the many well-known physical constants in science. The speed of light, which represents the absolute maximum speed that any object can travel, has a dimension of length/time, whereas the fine-structure constant, which quantifies the intensity of the electromagnetic force, has no dimensions at all.

The basic physical constant is a word occasionally used to describe the aforementioned universal yet dimensional physical constants. However, physicists now exclusively use basic physical constants for physical constants that lack dimensions, such as the fine-structure variable.

The physical constants addressed here shouldn't be confused with the other values also termed "constants,"

which are considered to be consistent in a specific context without even being basic, like the "time constant" distinctive of a certain system or material constants.

Each of the SI basic units has been described in terms of a physical constant as of May 2019. Consequently, the precise numerical values of the five constants, c (the speed of light in a vacuum), h (the Planck constant), e (the elementary charge), NA (the Avogadro constant), and kB (the Boltzmann constant), are known when stated in SI units. Fundamental constants include the first three, whereas NA and kB are purely technical; they do not explain any attribute of the universe but rather provide a proportional factor for establishing the units employed with many atomic-scale things.

5.4.1. Choice of units

The physical amount represented by a physical constant is independent of the unit system used to define the quantity; however, the calculated values of multidimensional physical constants are system-dependent. In contrast to its numerical value in a particular system of units, the phrase "physical constant" describes the physical quantity itself. In the SI system, the light's speed is specified as 299792458 meters per second, but in the natural system, it is defined as 1 Planck length per 1 Planck time. Light speed is a universal physical constant, although its numerical value is relative to the units used.

For instance, the proportion of proton mass to electron

mass is a non-dimensional physical constant since the two quantities have the same units. Through the technique of non - dimensional, every relationship between physical parameters may be described as a relationship between ratios that have no dimensions.

For physical numbers that, at least in the present state of knowledge, are considered unchangeable and non-derivable from more basic principles, the phrase "fundamental physical constant" is reserved. The acceleration of gravity G and the speed of light c are two well-known examples.

In the realm of basic physical constants, the fine-structure constant is the most well-known one. The value is the square of the expectation value in Planck units. When talking about whether or not physical constants may be derived, this number is often used as an example.

Nevertheless, thanks to the progress of quantum chemistry in the 20th century, a large number of dimensional less physical constants that had previously defied explanation were successfully calculated theoretically.

Thus, some theoretical physicists maintain optimism for rapid advancements in providing explanations for the values of additional non - dimensional physical constants.

If these constants had values different from what humans perceive, the Universe would look radically different. If the fine structure constant were to alter by just a few

percent, stars like the Sun would no longer exist. As a result, scientists have tried to provide anthropocentric explanations for the numbers behind some of the basic physical constants.

Natural units:

It would be possible to define continuous quantities of any size by combining universal physical constants, and this fact has been used by different systems of fundamental units of measurement. The resultant natural unit may be useful for a certain field of study depending on the selection and ordering of constants.

5.4.2. Classification schemes of three types of constants

A: characteristics that can be seen via the senses

B: typical of a certain kind of physical occurrence

C: Constants of Nature

The speed of light is a good example of how a physical constant can be reclassified from one classification to another as our understanding of its function evolves; originally classified as a class A constant (a feature of light), the speed of light was reclassified as a class B constant (a feature of electromagnetism) with the advent of classical electromagnetism and a class C constant (a feature of special relativity) with the advent of special relativity.

Chapter 6

Pollution control, Measures, and Standards

6.1. Activated Sludge Process (ASP)

Aeration as well as biological flocculation made up of both bacteria and protozoa is used in the activated sludge method which is a form of biological treatment wastewater technique. The process involves the utilization of air (or o_2) and microbes to biologically oxidize natural substances, with the latter ending up as waste sludge (or floc).

Following is a basic outline of how an activated sludge method for cleaning up carbonaceous pollutants is set up:

A vessel in which air (or O_2) is introduced into a mixed drink. The next step is a settling tank (sometimes called a "final clarifier" or "secondary settling tank"), where the biological flocs (the sludge blanket) are allowed to settle and the biological sludge is separated from the clean treated water. The sludge that isn't reused in the aeration tank is sent elsewhere for processing and eventually disposed of.

However, sludge thickening may develop, making activated sludge difficult to resolve and often affecting the quality of the final effluent in an unfavorable way. Skilled management is necessary for handling sludge bulking and maintaining the plant to prevent a recurrence, and full-time personnel of work may be necessary to enable prompt action. The Nereda process is a recent improvement on the traditional activated sludge method, yielding a particulate sludge that settles quickly and efficiently.

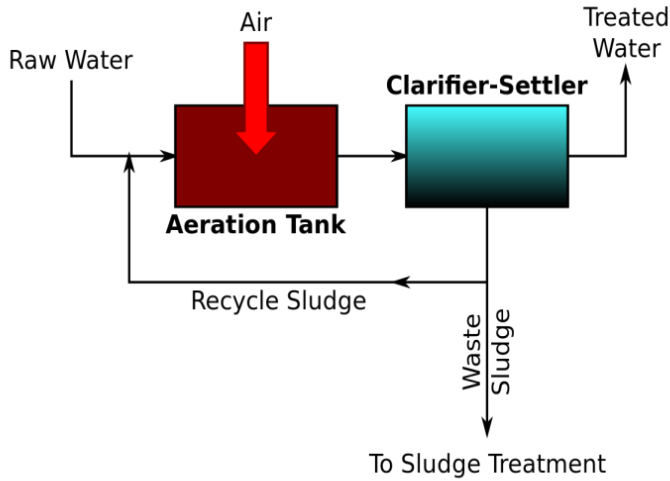

Figure 6.1: Diagram of an Activated Sludge Process.[*]

Package plants, oxidation ditches, deep shaft/vertical treatments, surface-aerated basins, and sequencing batch reactors are all examples of different sorts of plants (SBRs).

[*] https://en.wikipedia.org/wiki/File:Activated_Sludge_1.svg

Diffused oxygenation, surface aerators (cones), and even pure oxygen aeration are all examples of aeration techniques.

6.1.1. Purpose of Activated Sludge Process

The activated sludge procedure is a natural mechanism that may serve one or more of the following functions in wastewater or commercial wastewater treatment facility: Eliminating nitrogen and phosphorus from the environment by oxidizing carbon-containing biological matter and oxidizing nitrogenous materials, primarily ammonia and ammonia in biological matter.

6.1.2. Process description of Activated Sludge Process

Aerobic microorganisms are used for this procedure because of their ability to digest organic substances in sewage while also clumping together (through flocculation). This process results in a liquid with reduced amounts of suspended solids and other organic material, as well as flocculated particles that can be easily separated and filtered away.

Following is a basic outline of how an activated sludge procedure for cleaning up carbonaceous pollutants is set up:

- Air (or O_2) is introduced into the mixed liquid in an aeration tank.
- A settlement tank often called a final clarifier or

supplementary settling tank is used to separate biological sludge from clear treated water by allowing the flocs in the sedimentation tank to settle.

More work is required to treat nitrogenous materials or phosphate, with operations controlled to create an anoxic zone where phosphates can be solubilized in the reducing atmosphere and nitrogen oxides can be converted to ammonium ions.

1. **Bioreactor and final clarifier**

Biological floc is created by combining organisms with air or oxygen, which helps decrease the organic matter in screened and primary processed sewage or commercial sewage (wastewater). This substance, which is a brown floc in healthy sludge, is mostly made up of Saprotrophic bacteria but also contains a major protozoan flora component made up of amoebae, Spirotrichs, Peritrichs containing Vorticellids, and a variety of other filter-feeding species. Motile and sedentary Rotifers are also significant components. Sphaerotilus natans, Gordonia, as well as other mucilaginous filamentous bacteria, can grow in poorly managed activated sludge, creating a sludge that is hard to settle and, in extreme cases, can cause the sludge blanket to decant over the weirs in the settlement tank, severely contaminating the final effluent quality. Sewage fungus is a typical term for this material, although actual fungal populations are rare.

Mixed liquor is the usual name for wastewater combined with biological matter. At the end of the treatment process in an activated sludge factory, the surplus mixed liquor is released into settling tanks, as well as the processed supernatant is transported off to be processed further. Sludge that has sunk to the bottom of the tank is sometimes sent back upstream to be used as a fertilizer for the fresh wastewater being added to the tank. The floc collected in this manner is referred to as "return-activated sludge" (R.A.S.).

Using a membrane bioreactor to separate some sewage from the mixed liquor before treatment may minimize the amount of land needed for a wastewater treatment facility. As a consequence, the waste produced is more manageable and amenable to the activated sludge method of treatment.

Axial flow pumps are often used in wastewater treatment facilities to move nitrification mixed alcohol from the aeration region to the anoxic zone, where it may be denitrified. Internal mixed liquor recycling pumps are the common name for these devices (IMLR pumps). To accomplish denitrification, submersible mixers are used in anoxic zones to mix raw sewage, RAS, and nitrified mixed liquor.

2. Sludge production

The biologically active byproduct of activated sludge facilities is also known by the same name. To maintain stable biomass to food given in wastewater ratio, excess

sludge, also known as "excess sludge" as well as "waste-activated sludge," is eliminated from the treatment process. Sludge from secondary clarifiers is often combined with primary sludge before undergoing further sludge treatment, such as anaerobic digestion, hardening, dewatering, composting, and land applications.

Activated sludge treatment produces a constant volume of sewage sludge proportionate to the flow of wastewater entering the operation. Primary sludge out from main sedimentation tanks and residual activated sludge out from bioreactors are added to equal the total sludge output. About 70-100g/m3 of waste-activated sludge is generated during the activated sludge process (that is grams of dry solids produced per cubic meter of wastewater treated). The average density is 80 grams per cubic meter (2.2 ounces per cubic yard). In addition, most, but not all, activated sludge process designs include primary sedimentation tanks, which generate roughly 110-170 grams per cubic meter (3.0-4.6 oz/cu yd) of primary sludge.

3. Process control

Sludge blanket level, SVI (Sludge Volume Index), MCRT (Mean Cell Residence Time), F/M (Food to Microorganism), and the biota of activated sludge and the major nutrients DO (Dissolved oxygen), nitrogen, phosphate, BOD (Biochemical oxygen demand), and COD are all monitored as part of the standard process control

method (Chemical oxygen demand). The sludge blanket in the nuclear plant and clarifier system is measured up to three times daily in big plants, first from the bottom of the clarification tank to the height of settled solids in the water column.

The SVI measures how much space is taken up in the settled sludge by a certain amount of dry sludge waste. The MLSS (Mixed Liquor Suspended Solids) concentration is determined by dividing the volume of resolved sludge in a mixed liquor sample (in milliliters per liter of the sample) by the volume of the sample itself. The MCRT is calculated by dividing the total mass of mixed liquor suspension solids entering the aerator as well as the clarifier by the mass flow rate of mixed liquor dissolved particles exiting as had been and ultimate effluent in kilos or pounds per day. The F/M represents the daily food provided to the microorganisms relative to the microorganism mass being kept alive and oxygenated. This is determined by dividing the MLVSS (in kg or lb) by the daily BOD supplied to the aerator.

To adjust the concentration of sufficient in the mixed liquor, these controls allow for the waste or return of activated sludge (RAS).

6.1.3. Issues in the Activated Sludge Process

1. **Process upsets**

Sludge thickening may develop, making activated sludge

hard to settle and often affecting the quality of the final effluent in an unfavorable way. Skilled management is necessary for managing sludge bulking and maintaining the plant to prevent a recurrence, and full-time personnel work may be necessary to enable prompt action.

Toxic industrial pollutants released into treatment facilities meant for household sewage may disrupt operations.

2. Costs and technology choice

One more high-tech, energy-intensive, or "mechanized," but also more costly, method of treating wastewater is the activated sludge process. It's capable of delivering cutting-edge care.

A constant flow of electricity is required by activated sludge plants to run the aerators that return settled solids to the aeration tank intake and, in many instances, the pumps that transport discarded sludge and the final effluent. In certain plants, raw sewage is pumped up to the headworks so that there is enough elevation drop throughout the plant to provide a good release head for the industrial effluents. Technologies like the trickling filter treatment rely just on gravity and a significantly less amount of electricity.

6.2. Pollution control measures and standards

The word "pollution control" is often used in the field of environmental management. Emissions as well as effluents

into air, water, and soil must be contained. Excessive consumption, heat, farming, mining, manufacture, transportation, as well as other human activities, generate and disseminate waste products that, without pollution management, harm the environment. Preventing pollution and reducing waste is preferable to controlling it, according to the hierarchy of controls. Low-intensity development is a comparable method used in land development to reduce the amount of stormwater that flows off of buildings and streets.

To curb pollution, policies, laws, and enforceable economics tied to monitoring, transparency, and life-cycle assessment might be created and implemented. Despite the importance of issues like "informing intervention, influencing research, and guiding financing," a study found that they are not receiving the attention and action they need.

- **Practices**

1. Recycling
2. Reusing
3. Reducing garbage production
4. Mitigating
5. Reducing Emissions
6. Compost

6.2.1. Pollution Prevention Measures

There are a lot of things humans can't change in this world. Everyone is becoming so busy working to make ends meet

that, often neglect to live. Yet, humans only have one physical form, and if that form is no longer healthy, then nothing else will do. Consequently, it is crucial to take all feasible measures to regulate the modifiable aspects of pollution produced to avoid or reduce the health risks associated with exposure to pollution in the course of regular activities. Consider the following:

1. Make sure the places you spend the most time in at home and work are adequately ventilated with fresh air from the outdoors. For instance, try leaving the windows open. Keep them open for as long as possible. Leave the windows open while you're gone during the colder months if it's safe to do so. The presence of air will dilute and disperse any noxious gases that may be sneaking in volatile chemicals.
2. If your garage is linked to your home, make sure there are vents installed to let fresh air in. A door may connect the garage to the home; this door should not be left open. This will avoid or greatly reduce the amount of gasoline vapor that makes its way into the home.
3. Keep up with regular cleaning routines that include vacuuming, wiping, and dusting; dust contains particles ranging in size from all those visible to the naked eye to those that are tiny in scale. Heavy metals and organic compounds are only two examples of the kinds of contaminants that may be contained by such particles. Particles with a

diameter of fewer than ten micrometers may easily penetrate the human body, posing a serious health concern. It is thus crucial to always maintain a clean home environment.

4. Before relocating or investing in property, do an environmental impact assessment to ensure that you will not be living within a block of any major polluting sources. Also, it's preferable to live more than a mile away from any kind of municipal waste, foundry, or mine, as well as any kind of significant airport, seaport, or railroad station. Finally, even if everything looks fine after you've done all these inspections, you may want to test the soil and interior air from your possible new house just to be sure there is no pollution issue.
5. Only drink water from sources you can trust; in many cases, tap water is just as safe, if not safer, than bottled water because of frequent monitoring by local governments. Having a water filtration system in your house is recommended if you plan on using tap water for drinking. Compared to bottled water, the cost of these systems is far lower and they can be set up in a matter of hours. Still, you won't have to keep lugging around heavy bottles of water to keep up with demand. Never consume water from a domestic well unless it is frequently monitored and you are provided with monitoring data.
6. Before letting your children play outdoors barefoot,

get the soil tested if you live in a high-risk area. Many harmful chemicals that are discharged into the environment are taken up by the soil and stored there until they degrade. This is particularly important to keep in mind in desert regions, where water is in short supply and hence unable to be used for things like irrigation or washing contaminated materials away.

7. Water your garden regularly so that you may flush out the toxins that have settled on the soil's surface. Pesticides and herbicides are very harmful, even to people, therefore you shouldn't use them near your house. The chemicals they disperse onto plants and the soil may also enter the air we breathe.
8. Pesticides and herbicides are very harmful, even to people, therefore you shouldn't use them near your house. The chemicals they disperse onto plants and the soil may also enter the air we breathe.
9. Resist using air fresheners and other similar agents and instead take precautions such as storing your delicate clothing in plastic bags when not in use. If you really must use air fresheners or even other chemicals, do it only in closets located in rooms that you don't use often. You should also make sure your room has enough of fresh air and keep your doors shut.
10. The use of cleaning chemicals on carpets, furniture, etc., necessitates thorough ventilation thereafter. The identical holds for glues. This will guarantee

that any potentially harmful chemical concentrations in the surrounding air are quickly diluted and eliminated.

11. When sprinkling chemicals or dealing with paints, always wear a mask; as a general principle, if a chemical has a strong odor, it is harmful to your health, so taking as many precautions as possible to limit your contact is a good idea.
12. It is never too late to obtain legal counsel if, after taking the preceding measures, you discover that you have been polluted or are in danger. You might be eligible for financial compensation for the loss. Each situation must be evaluated independently. Get in contact with a specialist in environmental contamination for an opinion on your situation.

6.3. Trickling Filters

One method of cleaning water after it has been used is called a "trickle filter." Sewage or other wastewater runs downhill over a bed of pebbles, coke, pebbles, slag, polyvinyl chloride, sphagnum peat moss, ceramics, or plastics media, causing a layer of bacterial slime (biofilm) to form over the medium. Splashing, diffusion, and aeration if the filter system is porous all contribute to maintaining an aerobic environment in the bed. One of the earliest and best-understood treatment procedures is the use of trickling filters for wastewater.

The essential parts of a full trickling filter setup are:

- A filter media bed on which an accumulation of microorganism slime has been encouraged and grown;
- Bed of filter material enclosed in a container with a means of dispersing sewage flow across the medium,
- Treatment wastewater that has been filtered to remove any sludge and dispose of it properly.

A trickling filter is also known as a biofilter, a biological filter, a trickling biofilter, or simply a biological filter. Roughing filters, discontinuous filtration, packed medium bed filters, alternate septic tanks, percolate filters, connected cell growth, and fixed film procedures are all names that have been used to characterize these systems.

6.3.1. Process description

Sewage that has been settled often enters the main settlement tank at a higher level and flows downwards. The tank's supernatant is piped into a dosing device—typically a tipping bucket from which it is distributed to the filter's arms. Water is flushed through to the arms and out a set of angled holes at the bottom. This drives the arms to move in a circular motion, spraying the liquid all over the filter medium. The majorities are open to the elements and have no roofs.

Absorption as well as adsorption of organic molecules and

certain inorganic species, such as nitrate and nitrite ions, by the layers of microbial biofilm, are both involved in the removal of contaminants from the sewage water stream. A high surface-to-volume ratio is sought while selecting the filter material. Besides their exterior surface, most common materials also have a sizable interior surface area due to their porosity.

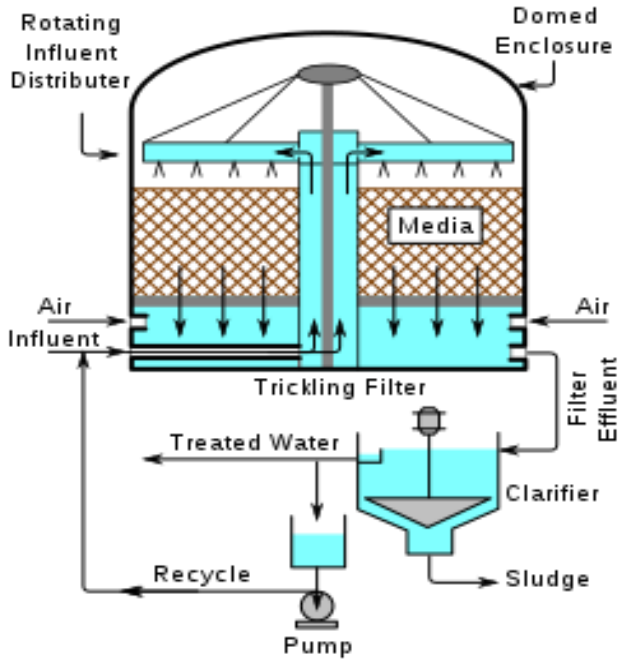

Figure 6.2: complete trickling filter system*

The biofilm layer, which is responsible for the biochemical organic compound oxidation compounds, needs dissolved oxygen, which is supplied by the wastewater as it flows

* https://en.wikipedia.org/wiki/File:Trickle_Filter.svg

over the medium, resulting in the release of carbon dioxide gas, water, and other oxidized finished goods. Secondary sludge is comprised of the biofilm layer, which gradually sheds into the flowing fluid as the biofilm becomes thicker. Once the sloughed film has been collected by a trickling filter, it is typically separated and removed using a clarifier as well as a sedimentation tank. High-density media filters like those made of sand, foam, or peat moss don't generate sludge that has to be disposed of, although they can need blowers, backwashing, or an anaerobic chamber anyhow.

Biofilm

The biofilm that forms in a trickling filter may grow to be several millimeters thick and is often a gelatinous matrix that may include several species of bacteria, including ciliates as well as amoeboid parasites, annelids, roundworms, mosquito larvae, and other microflora and microfauna. The filter might be a vermifilter if annelids are plentiful in the area. In contrast to ordinary biofilms, which can be thinner than 1 mm, this one is very thick. Both reductive and oxidative biological activities may be supported by the presence of anaerobic and aerobic zones within the biofilm. A "spring slough" occurs when the film becomes too thick because of the fast proliferation of microorganisms in the film, often during the spring.

6.3.2. Design considerations

Most trickling filters are circular, with a diameter of 10 to 20 meters and a depth of 2 to 3 meters. A layer of filter

material sits above a foundation of under-drains within a circular wall that is often made of brick. These under-drains have two purposes: to collect any water that could get caught in the filter media and to let air rise freely through the media. Two or more horizontally perforated pipes, extending to the media's edge, are mounted on a spindle that is centered above the filter medium. The holes on the pipes are oriented such that the whole assembly spins around the main axis as liquid flows from either the tubes and covers the entire surface area of the media. Sewage that has been settled is pumped through the spindle and into a central reservoir using a dispensing system, often a tipping bucket device on a set of miniature filters.

Rectangular filters with distribution arms powered by hydraulics or electricity are a practical solution for large filtering applications.

6.3.3. Types

Modest home septic tank outputs and extremely small rural waste disposal systems may be treated using single trickling filters. Many trickling filters run in tandem in larger centralized sewage treatment plants.

A single-pass system applies the treated water towards the trickling filter just once before discharging the water, whereas a multi-pass system cycles some of the treated water back through the system for further treatment in a closed loop. By encouraging nitrification within the aerobic

medium layer and denitrification inside the anaerobic septic tank, multi-pass systems improve treatment quality and help reduce Total Nitrogen (TN) concentrations. Filters in certain systems are arranged in two parallel banks, with a sediment stage in between, to allow wastewater to undergo filtration twice. To distribute the workload fairly, the filters are rotated every few days. Since most of the carbonaceous oxidant material is eliminated on the first passage through the filters, this treatment procedure may enhance nitrification and de-nitrification.

1. **Media types**

There is a wide range of filter media that may be employed to sustain the biofilm in a trickling system. Coke, lava, plastics matrix, accessible polyurethane foam, clinker, pebbles, sand, and geotextiles are typical examples of media. The ideal filter media doesn't deteriorate, has enough surface area for microbes to cling to, doesn't restrict air movement, doesn't become clogged up, can withstand all kinds of weather, and enables people to walk over the filter without any risk of mechanical damage. Forced aeration devices are necessary for certain residential systems, which will raise ongoing expenditures for maintenance and upkeep.

Many city dwellers were adversely affected by the stench, and a significant percentage of the waste disposal capacity was rendered inoperable as a consequence of the incident.

2. Industrial wastewater treatment

Customized trickling filters with plastic material and high flow rates may be used to clean industrial effluent. Trickling filters have been used to remediate wastewater from many different types of industrial operations. There are two varieties of these trickling filters used in industrial wastewater:

- Big concrete or plastic tanks with packaging material inside.
- Storage towers made of plastic packing material or another medium stacked vertically.

Low-cost plastic tower components are being used as trickling filter layers in tall towers as much as 20 meters.

As is the case with other trickling filter uses, the sludge shed by the microbiological slime layer connected to the trickling filter media is removed from the treated water output in a clarifier by the industrial wastewater trickling filter.

Oxygenated biofilters with plastic media in containers employing blowers to pump oxygen at the bottom of containers, either downstream or upstream of the wastewater, are an example of cutting-edge trickling filter technology.

6.4. Oxidation ponds

Secondary wastewater treatments, such as an oxidation

pond, lagoon, or water stabilization pond, process sewage and other waste from factories, homes, and other sources.

Solar energy is used with microorganisms like bacteria and algae to stabilize wastewater. The oxidation pond has an entrance and an outflow system and is built 1-1.5 m below ground. Wastewater treatment formerly included solar-powered bacterial and algal growth in a symbiotic relationship. It was later discovered that fungal development, in addition to the algae-bacterial relationship, may clean up industrial effluents and toxic waste.

The term "oxidation pond" is used to describe a kind of stabilization pond in which bacteria and algae play a key role in preventing the breakdown of municipal, commercial, and industrial waste. It appears to be a big pond, yet the water is only two to six feet deep. Again for secondary treatment of municipal and commercial wastes, an oxidation pond must have access to both sunshine and oxygen.

Inorganic and organic waste from the first treatment of sewage and industrial effluents, respectively, must be further processed. Wastewater that is disposed of directly into aquatic systems may have a negative impact on aquatic life including water quality.

6.4.1. Mechanism of Waste Treatment of Oxidation ponds

A basic comprehension of the following processes will

help you to grasp the mechanics or functioning of the oxidation pond:

The bacteria in the oxidation ponds will first oxidize the natural waste from the sewage, both residential and industrial. Bacteria produce carbon dioxide, water, as well as ammonia in this process.

For algae to flourish, sunshine is required. By breaking down organic materials, inorganic waste products are put to good use, and oxygen is released.

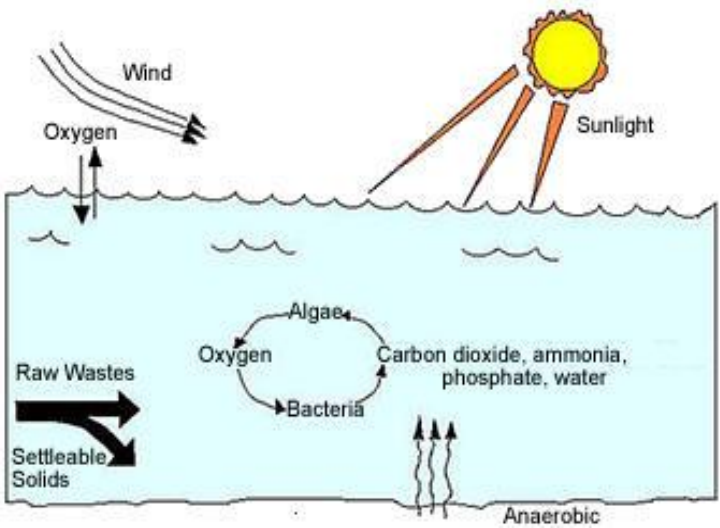

Figure 6.3: Oxidation ponds mechanism*

The needs of the algae as well as the bacterium are met through a mutually beneficial relationship. The bacteria react with oxygen the biodegradable organic material with

* https://water.mecc.edu/courses/ENV110/clipart/imageIH3.jpg

the oxygen generated by the algae. Carbon dioxide is produced when bacteria oxidize waste organic matter. In the long run, the algae use carbon dioxide to break down inorganic pollutants like phosphorus and nitrogen compounds. Due to the simultaneous occurrence of the reduction and oxidative reactions, oxidation ponds are also known as "Redox ponds." Oxidation pond sludge may be used as fertilizer in agricultural settings.

6.4.2. Process Involved in Oxidation Pond

The steps taken to reduce the complexity of industrial and household wastewater include:

- The oxidation pond receives the wastewater influents from either an industrial or household source via the intake system.
- The bacteria then consume the biodegradable organics, converting them into inorganic molecules through the release of carbon dioxide. Bacteria from the genera Achromobacter, Proteus, Alcaligenes, Pseudomonas, Thiospirillum, Rhodothecae, etc. are prevalent in the stabilization pond.
- The inorganic chemicals created by the oxidization of organic waste are used by the microalgae biomass in the oxidized pond, which is also exposed to sunlight and carbon dioxide. Algae from Chlorella, Euglena, Scenedermus, and Microcystis are the most prevalent types found in the stabilizing pond.

- The leftover inorganic and organic wastes become sludge at the stabilization pond's base. They are altered overnight in the lack of oxygen by anaerobic bacteria. The anaerobic bacteria first break down the insoluble waste products into organic acids like ethanol, which may be easily absorbed by the body. Anaerobic bacteria further decompose organic acids, releasing H_2S, NH_3, CH_4, CO_2, and other gases.
- A stabilization pond's output system is where the purified water goes after treatment. To remove sludge layers from the stabilization pond, dredging is often used. The algal and bacterium biomass may be separated by filtration, chemical treatment, or a combination of both.

6.4.3. Advantages of Oxidation ponds:

- As much as 90% of the biological oxygen requirement may be met by the stabilization pond on its own.
- You won't need any fancy gadgets to implement this strategy, and it'll provide good results.
- To treat home and commercial wastewater in tropical regions, oxidation ponds are a simple and efficient solution.
- Labor input for maintaining a stabilizing pond is minimal.
- It's a cheap option for dealing with wastewater from single-family homes or other relatively isolated facilities.

6.4.4. Disadvantages of Oxidation ponds

- More space is needed for the development of a stabilizing pond.
- The upkeep is complicated and requires special attention.
- If it isn't properly maintained, it may produce an unpleasant odor and become a breeding ground for mosquitoes.
- The possibility of effluent leakage into the groundwater resources, which might lead to groundwater contamination, must be taken into account.

6.5. Fluidized bed reactors

To carry out multiphase chemical processes, a fluid bed reactor (FBR) is a kind of reactor equipment. This reactor works by passing gas or liquid at high enough pressure and speed past a granular solid (often a catalyst), causing the solid to become suspended and operate like a fluid. Fluidization is the process through which an FBR gains many of its significant benefits. That's why FBRs may be found in so many different kinds of manufacturing settings nowadays.

6.5.1. Basic principles of Fluidized bed reactors

Porous plates, called distributors, are often used to support the solid glass substrate the catalytic materials on which the compounds react in a fluidized bed reactor. Once

within the distributor, the fluid is propelled upward through the solid. At low fluid speeds, the solids do not move as the fluid permeates the pores. A fluidized bed reactor describes such a device. At some point during the process of increasing the fluid velocity, the reactors will reach a condition where the pressure of the liquid on the solid is sufficient to counteract the gravity of the solid mass.

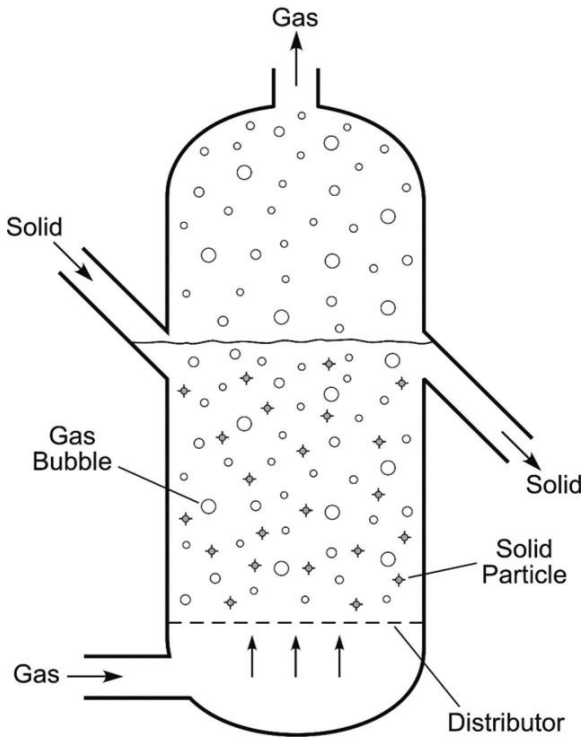

Figure 6.4: diagram of a fluidized bed reactor*

*https://en.wikipedia.org/wiki/File:Fluidized_Bed_Reactor_Graphic.svg

Minimum fluidization velocity marks the beginning of the fluidization process, also known as incipient fluidization. At this point, the fluids of the fluidized bed reactor begin to grow and swirl about, much like water in an unsettled tank or a pot of boiling water. Now there is a fluidized bed within the reactor. Different flow regimes may be seen in this reactor dependent on the operating circumstances and features of the solid phase.

6.5.2. Advantages of Fluidized bed reactors

The inherent benefits of the technology are primarily responsible for the rise in fluid bed reactor application in the modern industrial world:

- Particles in fluidized beds mix uniformly because the solid itself behaves like a fluid, eliminating the lack of mixing seen in packed beds. Since everything is thoroughly mixed, the final result is more consistent than it would be with certain alternative reactor designs. Improved fluid-solid contact is crucial to the efficacy and reproducibility of reactions, and this is made possible by doing away with an axial and radial gradient of concentration.
- Low and high-temperature gradients are both necessary for many chemical processes. Fluidized systems, such as FBR, eliminate the potential for local hot or cold areas inside the reaction bed, which may be a concern in packed beds. Product

degradation may occur in various kinds of reactors due to temperature changes at different locations, notably hotspots. Therefore, exothermic reactions are a good fit for FBRs. Researchers have also shown that FBRs have relatively high bed-to-surface heat transfer coefficients.

- Because of the fluidized bed design of these reactors, they may be operated in a continuous mode; in which product is continually removed and fresh reactants are added. Due to the elimination of starting conditions in continuous processes, producers may create their diverse goods more effectively while operating in a constant process state.

6.5.3. Disadvantages of Fluidized bed reactors

Like any other kind of reactor technology, the fluid bed reactor has several drawbacks that must be taken into account:

- The bed components in the reactor expand, necessitating a bigger reactor vessel than would be needed in a packed-bed reactor. The increased size of the vessel will result in a higher preliminary investment.
- Reduced pressure and the need for pumping are consequences of the greater fluid velocity needed to maintain the solid material in the reactor. There will be a rise in energy expenses due to the

increased pumping power required to do this. Deeper beds also need more pumping force due to the pressure drop they introduce.

- Particle entrainment occurs often in this kind of reactor due to the high flow velocities that exist there. When the fluid is drained from the reactor, it carries the trapped particles with it, which eventually need to be separated. Depending on the reactor's construction and purpose, this might be an exceptionally challenging and costly issue to solve. This may still be an issue even if we develop better methods of decreasing entrainment.
- Current knowledge is inadequate to describe the real behavior of the substances in a fluidized bed. Predicting and calculating the intricate mass and heat movements inside the bed is very challenging. A new facility for innovative processes is necessary due to the current level of ignorance. Scaling up from a pilot plant is challenging and not always indicative of the results seen in the whole operation.
- Wear and tear on the reactor vessel is a consequence of the fluid-like behavior of the small solid particles inside the bed. The response vessel and pipelines may need costly care due to this.
- Loss of fluidization pressure may cause a rapid decrease in the bed's effective surface area, leading to a pressure loss situation. This might be an annoyance, such as when resuming sleep after a

period of inactivity, or it can have more dire consequences, like runaway reactions, when heat transport is abruptly curtailed, as in the case of exothermic reactions.

6.6. Membrane bioreactor neutralization

Membrane separation and ultrafiltration membrane technology with activated sludge for biological wastewater treatment constitute a membrane bioreactor (MBR). Nowadays, it's often employed in industrial and municipal wastewater treatment. Submerged membrane bioreactors (SMBRs) and side stream membrane bioreactors (SSMBRs) are the two most common types of MBRs. In the first design, the membrane is positioned within the biological reactor, immersed in the effluent. In the latter arrangement, membrane therapy occurs after biological treatment but before the reactor.

The water shortage indicates the necessity to reuse water, after it has been adequately treated, thereby assuring environmental preservation. Among the treatment methods available to regenerated wastewater, those that employ membranes standout out for their potential to retain particles, and salts and even sterilize water, therefore creating water appropriate for reuse in agriculture and other purposes.

A membrane is indeed a substance that facilitates the selective passage of particular chemicals. The goal of using a membrane in a purifying water or regeneration system is

to allow water to pass through the membrane while trapping any impurities. Better pollutant retention may be achievable, depending on the membrane used. Different sorts of materials may be used to produce the membrane. However, the amount of materials that may be used to produce a membrane is different in the area of wastewater treatment than it is in other sectors owing to the many operating limits. Some of the needed features in membranes for treating wastewater include mechanical and chemical durability for five years of operation extremely acidic or basic characteristics or flexibility to function in a broad range of pH.

Organic composite membranes, as well as ceramic membranes, are the two most common kinds of membranes on the market. Polymeric membranes are among the most often used material in wastewater and water treatment. Due to its durability, chemical inertness, and mechanical strength, polyvinylidene difluoride (PVDF) stands out as the most widely used material of its kind.

Domestic wastewater treated using MBR procedures may provide effluent of high enough quality to be reused for urban irrigation after discharging into the ocean, a surface body of water, or a brackish river. Additionally, MBRs may be easily retrofitted into existing wastewater treatment facilities, allowing for an improvement in efficacy without having to completely replace them.

Reactor volume may be decreased while maintaining the same loading rate by using MBR procedures that run at greater Mixed Liquor Suspended Solids (MLSS) concentrations than traditional settling separation systems. There are two different types of membrane bioreactors (MBRs): inner, in which the membranes are an integrated part of the biological reactor, and outer stream, in which the membranes are a distinct unit process that requires an intermediary pumping phase.

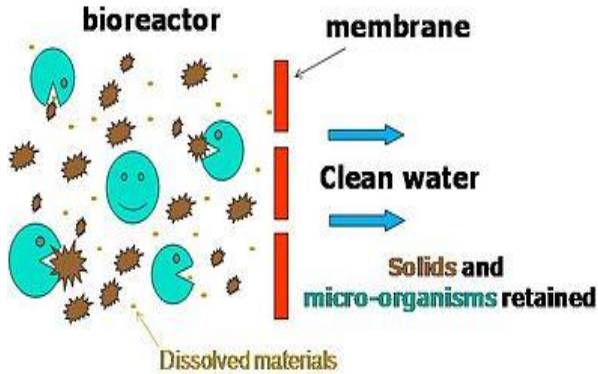

Figure 6.5: Membrane bioreactor (MBR) [*]

6.6.1. Advantages

- Reduced plant size is achieved by doing away with tertiary filtration and secondary clarifiers. Depending on the rules in place, it may be possible to remove or significantly decrease the size of additional process units like digesters or UV disinfection, further reducing the facility's footprint.

[*] https://en.wikipedia.org/wiki/File:MBR_Schematic.jpg

- Be customized to increase sludge age and reduce sludge output.
- Very good quality discharge
- Extremely high capacity for loading

6.6.2. Disadvantages

- Expensive to run and invest in (membranes)
- Increased membrane complexity as well as fouling
- Money spent on energy

6.6.3. Treatment Process and Basic Design Principles

A high degree of organic and suspended particle removal is achieved in membrane bioreactors by combining membrane filtration with traditional biological treatment (for example, activated sludge) procedures. These systems have the potential to remove nutrients at a high level if developed properly. The membranes of a membrane bioreactor (MBR) are immersed in a biological reactor that also contains oxygen. Porosities of the membranes range from between 0.035 and 0.4 microns (dependent on the manufacturer), placing them between microfiltration and ultrafiltration.

By filtering at such a fine level, sedimentation and conventional filtration methods employed in wastewater treatment are rendered unnecessary, allowing for the efficient passage of high-quality effluent through the membranes. The biological process may run at a greater mixed liquor concentration without the requirement for

sedimentation. Because of this, many old factories may be modernized without installing any additional tanks for the process. The mixed fluid is generally maintained in the range of 1.0-1.2% solids, four times that of a traditional plant, to enable adequate oxygenation and scouring around the membranes.

Current membrane configurations include five different types:

- A Hollow Fibre (HF)
- Spiral-wound
- Plate and frame, or flat sheet (FS), construction.
- Pinch-style filter cartridge with pleats
- Tubular

Pre-treatment

Fine screening is a crucial pre-treatment process for removing undesirable materials from the waste stream before it reaches the membrane tank. This ensures better sludge quality, lower operating costs, and a trouble-free operation by minimizing the formation of solids and protecting the membrane from harmful dirt and particulates.

Cost Considerations

Although the initial and ongoing expenses of an MBR system (membranes, oxygenation utilization, expert design, etc.) are more than those of traditional techniques, it seems that conventional systems are upgraded even

when they perform adequately. This may be connected to the growth of water costs and the necessity for water recycling as well as more strict standards on industrial effluent.

Operation and Maintenance

In most MBRs, weekly chemical upkeep cleaning takes 30-60 minutes, and biannual recovery cleanup happens when filtration becomes ineffective. Irrecoverable fouling is a deposit that can't be cleaned using current methods. Over several years of use, this fouling will accumulate and set limits on how long the membrane will last. Expert labor is required for all O&M duties.

Fouling

It isn't necessary to disconnect the membranes first from the membrane tank because advanced methods are maintained with chemicals. Sodium hypochlorite can be used to remove organic fouling, while oxalic acid can be used to remove inorganic fouling.

One of the major drawbacks of the MBR process is fouling, which develops as a result of the interactions between both the membrane as well as the mixed liquor. It is challenging to precisely localize as well as define membrane fouling due to the high degree of complexity inherent in the phenomenon and the wide variety of connections between the various causes of membrane fouling in MBRs. Membrane fouling is primarily caused by:

- Molecular-level adsorption
- Amplification of membrane-bound biofilms
- Inorganic matter precipitate
- Changes in membrane permeability with age

6.7. ETP sludge management

An effluent treatment plant, often known as an ETP, is a facility that cleans up wastewater from factories so that it may be reused or safely discharged.

- Influent: Raw sewage from a factory.
- Effluent: Water from factories that have been cleaned up.
- Sludge: The ETP is responsible for separating the solids from the wastewater.

6.7.1. Need of ETP

- Cleaning up industrial wastewater and reusing it is a priority.
- To lessen the need for drinkable water in manufacturing.
- To save money, we must stop buying water.
- To prevent incurring large fines and to comply with government standards for the emission or release of environmental contaminants from different industries.
- Protect against pollution, and aid in environmental sustainability.

6.7.2. Function of ETP

All major companies nowadays employ effluent treatment plants (ETPs) to purify their wastewater. ETPs are used by the world's foremost manufacturers of pharmaceuticals, chemicals, textiles, and other products that create wastewater to remove any contaminants. All of the businesses adopted these plants as part of their efforts to safeguard the environment and conform to regulations.

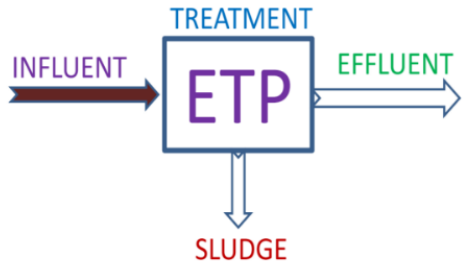

Figure 6.6: Effluent Treatment Plant[*]

6.7.3. Wastewater Sludge Treatment Process

A byproduct of wastewater treatment is sludge. Organic and inorganic components, a wealth of nutrient elements, organic compounds, and pathogens make up the bulk of its makeup. Therefore, effective treatment of such sludge is essential to reduce the negative effects it has on the environment. To assist you in better grasping the treatment methods and process prerequisites below is a high-level summary of the sewage treatment method:

[*]https://netsolwater.com/What%20is%20the%20function%20of%20ETP.png

Step 1 – Sludge Thickening

To begin the process of treating sewage sludge, a thickening phase is performed. Here, gravity thickening is used to lower the volume of the sewage sludge to a more manageable level. The sludge may also be thickened with the help of a technique called dissolved air flotation, which involves adding air bubbles to the mixture and letting the solid mass rise to the surface.

Step 2 – Sludge Digestion

Once the particles in the sewage sludge have been collected, the sewage process of digestion may begin. Sludge decomposition is a biological method that transforms organic materials into inert chemicals. This method not only reduces the overall bulk of solids but also kills any germs present, making dewatering simpler. Digestion of sludge occurs in two stages. As a first step, acid-forming bacteria are introduced to the dried sludge by heating and mixing it in a closed tank. Hydrolysis of the sludge's proteins and lipids yields water-soluble compounds, which the bacteria ferment into a wide variety of fatty acids. The methane is retrieved and either utilized to run the digestion tank again or transformed into electricity, depending on how much is recovered. Carbon dioxide (CO2) is released into the atmosphere.

Step 3 – Dewatering

Once valuable gasses and other byproducts have been

extracted, the residual sludge must be dewatered before being disposed of. Dewatered sludge, despite its frozen appearance, often includes a high concentration of water as much as 70%. That's why it's crucial to dehumidify the muck first. In most cases, sludge-drying beds are used, although this technique is labor-intensive and might take weeks to finish. These procedures may be sped up with the use of solid-liquid separation equipment, which is being included in an increasing number of waste management strategies. In contrast, the centrifuge is quickly replacing other techniques for dewatering sludge as a top choice. By centrifuging the sludge, all of the water may be extracted, facilitating more efficient and cost-effective solid waste management. The conveyor filter press and rotary vacuum filter are two further options.

Step 4 – Disposal

After proper dewatering, the sludge may be disposed of in a disposal facility or put to use as a fertilizer, based on its chemical makeup. If the sludge is just too dangerous to reuse or bury, it may be incinerated to create ash.

Even though sewage sludge is typically treated following a standard procedure, it is crucial to consider factors such as the source of the wastewater, the treatment method used to decrease the wastewater to sludge, and the potential byproducts that may be recovered from it to further use before deciding on a sludge treatment regimen. This can help you maximize productivity while also cutting

expenses by repurposing items that would otherwise be thrown away.

6.8. Digesters

A digester is a large tank used for performing chemical or biological processes. Depending on its function, a digester, which is a kind of tank, may be either large or small. The volume of a home fermenter for a small household may be no more than a cubic meter, whereas that of an industrial-scale machine can easily exceed 5,000 cubic meters. Several dozen of cubic meters is the normal capacity of a fermenter on a ranch or farm.

6.8.1. Anaerobic Digestion Working

The fundamental concept of all anaerobic digesting processes remains constant.

Loading

An anaerobic, or oxygen-free, cylindrical jar receives the homogenized substrate, which is obtained by crushing the solid or liquid particles. Grain (the most efficient), jaggery, animal fat, cow and poultry dung, domestic waste, and sewage sludge are all examples of feedstocks.

Fermentation

Typically, the biomass is burned to between 37 and 38 degrees Celsius (occasionally higher than 50 degrees Fahrenheit) while being continually agitated. Biogas is

produced from fermented biomass after a minimum of 20 days of bacterial-induced chemical changes. Like fossil fuels from a hydrocarbon source, biogas has 40–70% methane (CH4). Carbon dioxide (CO2) and trace levels of sulfur are all that is left in the gas tank.

Biogas uses

Biogas may be used locally in a co-generation engine to generate heat and electricity, or the methane can be filtered using membranes and used as transportation fuel or injected into the common natural gas network.

Removal

It is common practice to apply the byproduct of substrate conversion, known as the digestate, to agricultural fields as a nutrient-rich soil amendment. A biogas plant consists of a digester, a facility to store and sort the waste products, a gas holder to store the biogas, a cogeneration unit to generate heat and electricity, and a control center to manage the different processes. In comparison to the need for natural gas, the output of biogas has not increased.

6.8.2. Different Types of Anaerobic Digesters

Biogas Plant

Hundreds of towns' worth of food and paper scraps, as well as other industrial byproducts, are processed at once in a large-scale biogas facility. Organic stuff must be separated from inorganic garbage like plastic and

packaging, hence sorting is required. Macerating and pumping the organic material into steel towers that can reach heights of over 30 meters is the next step. A gas holder is used to collect and store the biogas. In most cases, a biogas facility will be situated close to the industrial site where it will be supplied with gas or power.

Wastewater Plants and Sewage Treatment

Pollutants in sewage from homes and factories are cleaned up by water treatment facilities. In this process, agricultural wastes and manure feedstocks are removed from the equation, allowing the purified water to be discharged back into rivers while the thick sludge may be used to make biogas. Sludge in a constant flow system is handled in giant containers with a metal dome on top, and the sludge is continually churned by massive machinery called agitators.

Micro-Scale Anaerobic Digestion

The power output of less than 50 kW makes small-scale units ideal for residential, commercial, municipal, and industrial use. Some two-part systems made of plastic, one for gas storage and one for fermentation may be purchased for a few hundred euros. To generate power, even a small digester may be coupled with a generator. Micro-scale digesters have the problem of needing constant maintenance and a starting period of several weeks. Homemade units are often used for heating, cooking, and lighting in regions with limited access to electricity.

6.9. Up-flow anaerobic sludge blanket reactor

The UASB reactor, or up-flow anaerobic sludge blanket (UASB) technique, is a kind of anaerobic digester used to treat wastewater.

The UASB reactor is a methane production (methane-producing) digester that originated from the anaerobic classification. Expanded Granular Sludge Bed (EGSB) digesters are an alternative technique with some similarities to UASB.

6.9.1. Process description of up-flow anaerobic sludge blanket reactor

An anaerobic process is used by UASB to create a layer of granular sludge that floats in the tank. The wastewater is digested and destroyed by anaerobic bacteria as it rises through the blanket. With the help of flocculants, the upward flow and the settling act of gravity hold the blanket in suspension. At around the three-month mark, the blanket reaches full maturity. Bacterial colonies grow on the surfaces of the sludge particles that form. Only microorganisms capable of adhering to each other will survive and grow in the lack of a support matrix caused by the flow conditions. Eventually, the clumps coalesce into "granules," which are compact biofilms.

As a byproduct, biogas with such a heavy proportion of methane is created; this biogas may be caught and utilized as a source of energy, generating energy for export and

covering its operating power. To keep the sludge blanket in place and prevent it from being washed away and losing its effectiveness, the technology must be constantly monitored after it is put into action. The waste heat from the creation of energy may be used to warm the fermentation vats.

With the sludge covered, the digesters may have a longer retention period for both the solids and the hydraulic liquid. High-digestibility solids may stay in the reactor for up to 90 days. Liquid waste streams containing sugars may be treated to produce gas, which can then be released from the system in much less than a day. Generally speaking, UASB reactors work best with low-strength wastewater streams (3% TSS) that include particles >0.75mm in size.

6.9.2. Function and Application Up-flow anaerobic sludge blanket reactor

- Businesses devoted to brewing and serving alcoholic beverages
- The Brewing, Distilling, and Fermented Sector
- The Food Market
- Paper as well as pulp.

6.9.3. Advantages of up-flow anaerobic sludge blanket reactor

- Biofuel, a significant source of energy, will be created throughout the primary treatment and captured for later use.
- When opposed to an aerobic process, which relies

on the wastewater's cellular energy for new cell development, anaerobic digestion uses far less of the wastewater's cellular energy, resulting in much less bio-solids waste.

- The treatment method requires little energy.
- Reduced need for nutrition.
- The system may be turned off for long periods without suffering significant damage; and
- Capable of withstanding the stresses of an organic shock adequately.

6.9.4. Disadvantages of up-flow anaerobic sludge blanket reactor

- Surface river flow quality cannot be achieved without post-treatment after anaerobic treatment;
- The production of reduced sulphur compounds raises concerns about corrosion, odor, and safety.
- More time is needed to get going.
- The anaerobic process can only be carried out in a very narrow temperature range (between 15 and 35 degrees Celsius), making it unusable in colder regions of the world during the winter.
- Some tools (pH meter, thermometer, etc.) and trained personnel are required for keeping tabs on the reactor's interior environment. To put it simply, it's expensive.

6.10. Sequencing batch reactors

To treat wastewater, activated sludge processes like sequencing batch reactors (SBRs) may be used. SBR

reactors are used for the batch treatment of wastewater, such as sewage or the product of anaerobic digesters and mechanical biological water treatment facilities. Biochemical oxygen demand (BOD), as well as chemical oxygen demand (COD), are indicators of the amount of organic matter in wastewater, and both BOD and COD may be reduced by introducing oxygen to the combination of wastewater with activated sludge. Effluent disposal to surface waterways or land application is also possible after treatment.

The fundamental operation of SBRs is consistent regardless of the variety of configurations that exist. The setup has many tanks that may function either as plug flow or fully mixed reactors. Raw sewage (influent) flows into one end of the tanks and cleaned water (effluent) flows out the other; this is known as a "flow-through" system. When using a system with several tanks, one tank might be aerating and filling while the other is in settle/decant mode. The bio-selector is a portion of certain systems' tanks that contains a series of barriers or hurdles that guide the flow from one of the tank's sides to the other or from beneath and over a series of baffles. By doing so, the biological digestion process may begin before the liquor hits the main section of the tank by combining the entering Influent with the returned activated sludge (RAS).

6.10.1. Treatment stages

There are five stages in the treatment process:

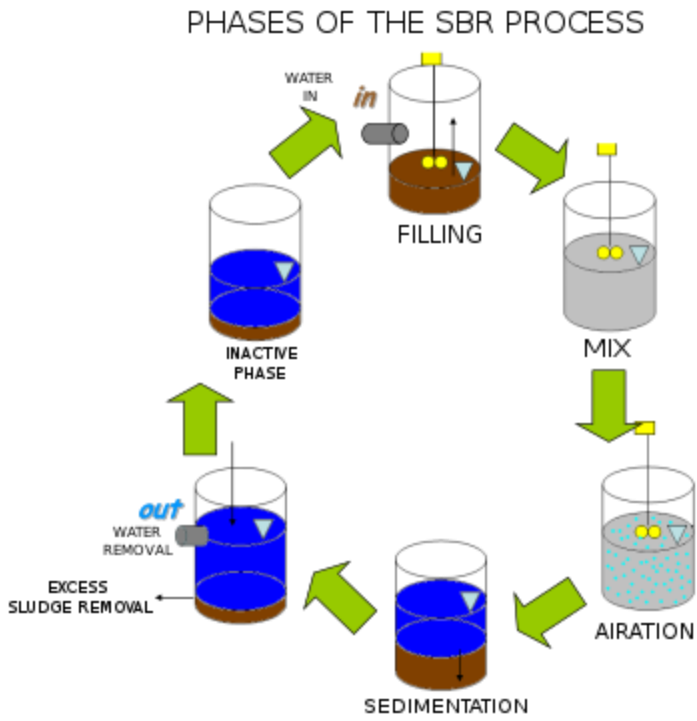

Figure 6.7: The phases in the operation of an SBR[*]

- Fill
- React
- Settle
- Decant
- Idle

The tank is filled with no air supplied yet, and the intake valve is opened to allow for mixing by mechanical methods during this filling process. This is the anoxic

[*] https://en.wikipedia.org/wiki/File:Sbr_phases.svg

phase, another name for it. To aerate the combined liquor in the second step, either mechanical pumps mounted to the bottom of the tank or fine bubble diffusers are used. The third phase sees the cessation of aeration and mixing, resulting in the precipitation of suspended particles. At this point, the "clean" residual liquor is released from the tank via an output valve.

6.11. Hybrid reactors

By adding carriers to the aeration tanks, researchers were able to create a hybrid biological reactor (HBR) that incorporates a new period of attached biomass into a traditional suspended-growth system (active sludge process). By incorporating porous materials into a conventional activated sludge unit, a unique hybrid biological reactor was created which included both suspended as well as attached-growth biomass and was employed for the treatment of residential wastewater.

To create an anaerobic digester, engineers combined UASB reactors with an anaerobic filter, creating a hybrid reactor. This hybrid is a cutting-edge configuration that enables enhanced solid retention time during wastewater treatment. Each day, the reaction chamber must be emptied of this wastewater to avoid an explosion. The volumetric load capacity of the anaerobic digestion system is intermediate.

The ADI hybrid reactor integrates up-flow anaerobic sludge bed (UASB) as well as up-flow fixed-film reactor

(FFR) processes while preserving the strengths of both technologies. The biodegradable organic waste in the wastewater is digested by a layer of anaerobic biomass in the reactor's bottom section, which works as a UASB. A cross-flow type medium is located in the top part of the reactor, giving the fixed-film bios plenty of room to spread out and multiply. Through a lamella-plate method of clarifying, the medium additionally captures particles from the sludge bed and the raw influent, before redistributing them to the sludge bed.

A two-stage reactor may be constructed to produce higher-quality effluent in situations calling for very high removals. This two-stage system has a pair of parallel reactors of similar size that switch roles as leader and follower at regular intervals. High quantities of dissolved organics and low amounts of solids are effectively treated by this cyclic operation in wastewater streams.

- Continually satisfies discharge standards
- Create renewable electricity from compostable garbage (heat and power)
- Continual solids retention and a high biomass stock
- Superior peak-load process stability.
- Large-surface-area, cross-flow medium for solids retention
- encourages the expansion of living tissue
- Permits a Rapid Rate of Loading
- Liquid waste that may be spread on the ground
- Due to the lack of complex machinery and moving

components, less upkeep is needed.

- Program for the Adaptive Disposal of Sludge
- Process control using historical data trends
- The cover allows for simple access to testing and upkeep

6.11.1. Features of Hybrid Reactors

Costing savings

- Help reduce energy expenses.
- Environmentally friendly energy use
- Much more efficient than aerobic systems in terms of energy use
- Reduce the plant's reliance on fossil fuels by recovering energy from biogas.
- Cost-sharing for wastewater treatment should be ended.
- Chemical use should be minimized or stopped altogether.

Environmental benefits

- Maintain consistently compliant discharge standards
- Reclaimable green energy from compostable garbage (heat and power)
- With its high nutritional content, waste sludge may be used as a liquid fertilizer on agricultural land.
- Strengthen water security everywhere, locally, and globally

Process advantages

- Continual solids preservation and a high biomass stock
- Superior peak-load process stability.
- Large-surface-area, cross-flow medium for solids preservation
- Encourages the expansion of living tissue
- Enables rapid loading speeds

Simplified operation & maintenance

- Due to the lack of complex machinery and moving components, less upkeep is needed.
- Low levels of operator involvement
- Program for the Adaptive Disposal of Sludge
- Process control using historical data trends
- The cover allows for simple access to testing and upkeep

6.12. Biological Treatment of Air Pollution

Aerobic microorganisms, primarily mesophilic bacteria, which consume both inorganic and organic chemicals in the waste gas, are essential to the biological remediation of air pollution. Microbes break down the contaminants into harmless byproducts like carbon dioxide, water, as well as salts.

In addition to one's historical use in places like livestock processing facilities to reduce unpleasant odors, biofilters

are now also being implemented in composting facilities to reduce ammonia and in brewpubs, production lines, plastics, papers, and petrochemical plants to reduce volatile organic carbon emissions. Biofilters have also been used to extract vapors from polluted groundwater and soil.

6.12.1. Biofilter

The cheapest and most straightforward biological therapy is this one. A layer of composted, tree trunks, moss, heather, or dirt approximately 1m thick is the principal component of this system, and contaminated air is forced through it. Biofilter beds include a rich culture of organisms that digest the gaseous contaminants.

Most biofilter systems come in the form of towers; they are enclosed, vertical structures. The design has advantages over open chambers in terms of process control and emissions monitoring. Without proper regulation of the incoming airflow distribution as well as humidity, the bed will act only as an adsorbed filter and ultimately get clogged. The ideal conditions for the incoming gas include a temperature range of 10-40 degrees Celsius, high humidity content, and low dust content. Depending on the amount of contamination, these devices may endure anywhere from one to seven years.

6.12.2. Bioscrubber

The two main components of a bio scrubber are a scrubber

as well as a biological wastewater treatment basin, and they work together to reduce air pollution and treat wastewater. Scrubbers are constantly drawing in oxygen and absorbing the waste gases that are soluble in water.

The basin unit, typically the activated sludge basins of a sewage treatment plant, is where the biological oxidation takes place. Bioscrubbers are used in situations where the acids created during H2S and NH3 elimination would be detrimental to a biofilter bed. Bioscrubbers are also being utilized to get rid of chlorinated organic compounds, in addition to hydrocarbons. There are two basic kinds of bio scrubbers:

Activated-sludge scrubber- In a simple and useful packed column tower, a solvent takes in the gaseous contaminants. In most cases, a combination of water and sludge is used as the absorption solution (1-10 g sludge per liter of water). The solution is biodegraded in a sedimentation tank after being absorbed in the column. The packed column receives recycled, filtered liquid from the sedimentation tank.

Trickling-filter scrubbers- Countercurrent scrubbers work similarly as activated sludge scrubbers in that they move gaseous impurities into the liquid phase. Scrubber wastewater is dispersed over a trickling filter instead of being put into such an activated sludge pond. It's more precise than activated sludge scrubbers, which is a big plus for the technique.

Compared to other purification methods, biofiltration's main benefit is its low cost of operation. Scrubbing has around a 300 percent higher operational cost than biofiltration, incineration about 1,300 percent higher, and carbon adsorption around 1800 percent higher. A biotower's initial investment is about the same as that of competing treatment methods. Another benefit of bio-scrubbing is that it leaves behind no residues that would have to be cleaned up afterward.

6.12.3. Biotricking filters

Biotricking filters are indeed a cutting-edge method of biological purification. While biofilters are effective, bio trickling systems are much more so since they can handle more pollution at once.

From a physical perspective

Similar in appearance to chemicals or water scrubbers, this system relies on microorganisms in the recirculation water as well as on the surface of the step towards providing to perform the oxidizing activity, rather than chemical reagents.

The medium used in Biotrickling filters is often made up of inorganic, naturally occurring minerals or inorganic, manufactured synthetic media with a high specific area, and it plays a crucial role in providing an optimum habitat and circumstances for the development of micro-organisms.

Calcium carbonate within the shell plays a key role in the system's efficacy against high concentrations of hydrogen sulfide.

6.13. Regulatory framework for pollution monitoring and control

People's long-held belief that we must choose between improving the environment and expanding the economy has given way to the view that these two goals are inherently complimentary as environmental awareness has expanded. The present environmental consciousness is not new; environmental concerns have always played a vital role in Indian culture. India's international obligations, as well as its constitutional, legal, and policy framework, all reflect the country's longstanding recognition of the need of protecting and sustainably using the planet's natural resources.

Several environmental laws had been passed in India before its independence in 1947, but it wasn't until the United Nations Conference on the Human Environment that any real momentum was gained toward creating a comprehensive framework. In 1972, the National Council for Environmental Policy and Planning was established as part of the Department of Science and Technology in response to this announcement. The Council's work on environmental preservation was institutionalized in 1985 when it was elevated to the Ministry of Environment and Forests (MoEF), the country's top administrative department.

The 42nd Amendment, which included environmental protections in the Directive State Policy Principles as well as Fundamental Rights and Duties, provided constitutional recognition for environmental concerns in the wake of the 1976 Stockholm Conference.

There has been a rapid expansion of environmental protection laws in the nation since the 1970s. The Ministry of Environment and Forests (MoEF) and the pollution control boards (CPCB i.e. Central Pollution Control Board and SPCBs i.e. State Pollution Control Boards) combined constitute the regulatory and administrative heart of the sector.

To accompany the provisions of the law, a guideline has been drafted. In 1992, the Ministry of Environment and Forestry (MoEF) issued the Policy Statement for Abatement of Pollution as well as the National Conservation Strategy and Policy Statement on Environment and Development to create and support efforts for the conservation and enhancement of the environment. The Environmental Action Programme (EAP) was established in 1993 to enhance environmental services and incorporate environmental issues into development plans.

6.13.1. Legislation for environmental protection in India

Water

The Indian Council of Medical Research establishes

guidelines for safe water use. These are quite similar to the criteria established by the WHO. Recently, water quality criteria for coastal or marine outfalls have been set by the Indian Standard Codes, which control the release of industrial effluents. Specific requirements for effluent discharges from sectors like iron and steel, aluminum, paper, and pulp oil refineries, petrochemicals, and thermal power plants have been created in addition to the general norms. Following is a list of laws enacted to reduce water pollution.

Water (Prevention and Control of Pollution) Act, 1974

The first serious effort by India to address environmental concerns across the board, this Act was passed in 1986. The Act establishes fines for noncompliance and bans the discharge of contaminants into water bodies over a certain level. In 1988, the law was changed so that it more closely followed the Environmental Protection Act of 1986. It instituted the Central Contamination Control Board (CPCB), which established guidelines for the management of water pollution. The SPCBs (State Pollution Control Board) carry out their duties at the state level under the guidance of the CPCB and the respective state government.

Water (Prevention and Control of Pollution) Cess Act, 1977

Water used by businesses and government agencies is subject to a cess that will be collected under the terms of

this law. The plan's end goal is to increase the capacity of federal and state agencies to combat water contamination. The Water (Prevention and Control of Pollution) Cess Rules, drafted in 1978 in response to the act, specify the kind and placement of water meters that all water users must have.

Air

Air (Prevention and Control of Pollution) Act, 1981

The Act of 1981 set criteria for ambient air quality to reduce the health risks connected with air pollution. The Act establishes procedures and tools for managing and reducing air pollution. The Act's goal is to reduce air pollution by controlling the production and use of polluting equipment and by outlawing the use of harmful fuels and chemicals. An industrial facility inside a pollution control area must get approval from the relevant state bodies before it may be established or operated under the Act. The boards are also responsible for inspecting production processes and pollution control equipment, as well as testing the air quality in designated air pollution control zones.

The CPCB announced NAAQS for main contaminants in April 1994. To safeguard people, plants, and property, these are the minimum acceptable limits of air quality. To protect vulnerable populations, the NAAQS establishes zone-specific guidelines for a variety of settings, including industrial, residential, rural, and urban. Iron and steel

mills, cement factories, fertilizer industries, oil refineries, and the aluminum sector all have their own sets of emission requirements. Standards for environmental quality in India are generally in line with those in both developed and developing nations.

The Air (Prevention and Control of Pollution) Amendment Act, 1987 was passed to provide the national and state pollution boards with the authority necessary to respond to critical situations. The boards have the authority to act swiftly in such situations and seek reimbursement from the offenders for any costs spent as a result of their actions. The authority to revoke permission for failing to meet requirements set out in a permit has also been reinforced in the Air Act Amendment.

The Air (Prevention and Control of Pollution) Rules were drafted in 1982 and detail how board meetings are to be run, who has voting rights, what constitutes a quorum, how minutes should be recorded, and other administrative details. They also outlined the procedures for consulting experts, the types of issues that need their attention, and the associated costs.

The Atomic Energy Act of 1982 was passed to address radioactive waste and works in tandem with the aforementioned statutes. To ensure adequate packing, labeling, and transporting of hazardous wastes, the Motor Vehicles Act was passed in 1988. The Environmental Protection Act of 1986 also includes provisions for

reporting various types of vehicle pollution. In 1990, the government announced new mass emission rules, which were later tightened in 1996. In 2000, these criteria were updated once again, and for the very first time, individual legal responsibilities for car buyers, automakers, and regulators were established.

Chapter 3
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Computer-assisted Potentiometric Analysis of L-leucine and Isoleucine Protonation Equilibria in SLS-water System

M. Sudha [a], M. Ramanaiah [b], P. Surya Sunitha [c], Y. Triveni [d] and B. B. V. Sailaja [e*]

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ABSTRACT

At 303 K, the effect of sodium lauryl sulphate (SLS) on the dissociation equilibria of L-leucine and Isoleucine was investigated at varying strengths (0.0, 0.5, 1.0, 1.5, 2.0, and 2.5%) of SLS liquid containing 0.16 mol dm^{-3} NaCl. The dissociation constants were calculated with the help of the programming language MINIQUAD75, and the models that provided the best fit were identified with the use of crystallographic R factor, χ^2, skewness, and kurtosis for the purposes of statistical analysis. The values of these dissociation constants shift in micellar medium compared to those in pure water. In the case of charged micelles, the discrepancies in values have been attributed to the solvent characteristics of the interfacial and bulk phases, which include contributions from the electrostatic potential of the micelle surface. The trend of log values of step-wise dissociation constants with medium composition has been characterized using electrostatic and non-electrostatic forces acting on dissociation equilibria. Further, species abundances, dissociation dynamics, and the influence of essential factors on dissociation constants are displayed.

Keywords: Dissociation constants; MINIQUAD75; sodium lauryl sulfate; L-leucine; isoleucine.

[a] Department of Humanities and Sciences, School of Engineering, Nalla Narasimha Reddy Education Society's Group of Institutions Integrated Campus, Hyderabad - 500088, India.
[b] Department of Chemistry, Aditya Institute of Technology and Management, Tekkali-532201, India.
[c] Department of Chemistry, Government College for Women(A), Srikakulam-532001, Andhra Pradesh, India.
[d] Department of Chemistry, Dr. Lankapalli Bullayya College, Visakhapatnam- 530013, India.
[e] Department of Chemistry, Andhra University, Visakhapatnam-530003, India.
**Corresponding author: E-mail: sailajabbv.chem@gmail.com, ramanaiahmalla4@gmail.com;*

1. INTRODUCTION

The anionic surfactant sodium dodecyl sulphate (SLS) or sodium lauryl sulphate (SLS) dramatically affects the bulk characteristics of biological mechanisms. They may dissolve ions and molecules, concentrate them, and compartmentalize them [1]. There are numerous industrial applications for aqueous micellar media, including pharmaceuticals, analytical chemistry, chemical synthesis, and others. Micelles are also commonly employed in energy storage systems [2,3]. Amphiphilic molecules, which include both hydrophobic and hydrophilic groups, combine in water above a predetermined concentration to form micelles [4]. Micellar systems have the ability to alter acid-base equilibrium. This change in the balance of chemical forces can be explained by variations in the characteristics of the bulk solvent and the interfacial region, as well as by the electrostatic field effect of the charged interface [5], which perturbs the acid-base equilibrium. Using potentiometry, the equilibrium reaction of substituted benzoic acids in various surfactants have been studied [6]. In anionic micelles, their pKa values shift to approximately 0.5-3.0, as demonstrated. The acido-basis equilibrium of a compounds in aqueous surfactant liquids has been investigated [7]. This study examines the impact of anionic surfactant on the dissociation equilibria of two physiologically relevant compounds, namely L-leucine and Isoleucine, in SLS.

The study of chemical equilibria reveals the nature of aqueous systems by explicating the dynamics occurring in solutions [8]. Equilibrium systems provide insight into the types of complexes that form based on the pH of the surrounding environment, allowing the identification of compounds with potential biological features. This information can be utilized to synthesize specific structures found in solutions and to build novel chemical compounds with medicinal and pharmacological applications. The complexation process determines the biological characteristics of ligands and metal ions [9-13].

2. EXPERIMENTAL

2.1 Chemicals and Standard Solutions

L-leucine and Isoleucine (E-Merck) solutions (0.05 mol dm^{-3}) were produced in deionized water by keeping a concentration of 0.05 mol dm^{-3} hydrochloric acid to improve dissolution rate. As obtained, sodium dodecyl sulphate (E-Merck) was utilized. 0.2 mol dm^{-3} of hydrochloric acid (E-Merck) was produced. To maintain the ionic strength of the titrant, 2 mol dm^{-3} of sodium chloride (E-Merck) was made. 0.4 mol dm^{-3} of sodium hydroxide (E-Merck) was produced. All solutions were standardized utilizing standard procedures. The data were subjected to a one-way classification analysis of variance to analyses errors in concentration determinations [14-18]. Using the Gran plot method [19-24], the strength of base and acids were calculated.

2.2 Methods and Equipment for Analytical Research

Titrations of alkalis were carried out in fluids comprising different compositions of sodium lauryl sulphate while keeping 0.16 mol dm^{-3} ionic strength with NaCl at

303±0.05K. Utilizing an ELICO LI-120 pH meter. The pH meter was calibrated using various standard solutions. The titrant in each titration was roughly 1 mmol of HCl. The ligand concentrations in the titrants ranged from 0.25 to 0.50 mmols. The pH sensing glass electrode was homogenized in a harmless electrolyte solution of sodium dodecyl sulphate and water over the course of several days. By periodically titrating a strong acid against an alkali, we can ensure that the glass electrode has fully equilibrated. The pH sensing glass electrode was replenished with an SLS-water solution of the same percentage as the titrant. The analytical procedures and reaction apparatus have been described in detail elsewhere [25-28]. Fig. 1 demonstrates the alkalimetric titration curves.

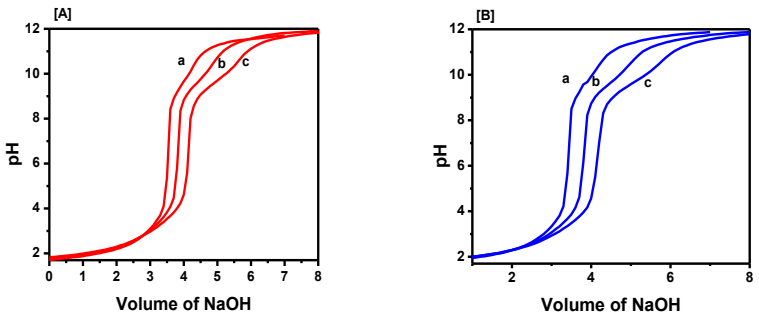

Fig. 1. Experimental graphs in 1.0% w/v SLS concentration: [A] L-Leucine [B] Isoleucine; (a) 0.25, (b) 0.375 and (c) 0.50 mmol, in that order

2.3 Modeling Strategy

Using the program SCPHD [29-31], the estimated dissociation constants of L-leucine and Isoleucine were computed. The optimal chemical model for each analyzed system was determined using the non-linear least-squares computer software MINIQUAD75 [32] which takes advantage of the restricted least-squares approach in the initial refinement and the Marquardt algorithm's dependable convergence. On electrostatic grounds, the fluctuation of stepwise dissociation constants (log K) with the strength of the solvent was investigated for interactions between different types of solvents and different types of solvent-free solutes.

3. RESULTS AND DISCUSSION

3.1 The Role of Secondary Formations

The role of secondary formations, such as the average number of protons bound per mole of ligand ($\bar{n}_H$)and the number of moles of alkali used per mole of ligand (a), can be used to calculate the number of equilibrium states. If there is

no production of polymeric species, plots of $\bar{n}_H$ against pH for various strength of the ligand should go together. Overlapping L-leucine and Isoleucine production trends (Fig. 1) exclude polymerization of the ligand molecules.

The dissociation constants of the ligands are represented by the pH values at half-integrals of $\bar{n}_H$. Two half integrals (1.5 and 0.5) for L-leucine (Fig. 2[A]) and isoleucine (Fig. 2[B]) emphasize two dissociation-association equilibria within the pH range of our study. The number of these equilibria correlates to the number of plateaus in the formation curves.

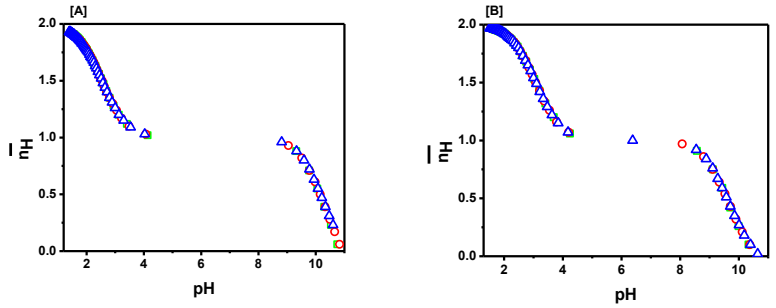

Fig. 2. Graph of $\bar{n}_H$ versus pH in 2.0 % w/v SLS concentration; [A] L-leucine [B] Isoleucine, (Δ) 0.25, (○) 0.375, and (ϒ) 0.50 mmol, in that order

Plots of the parameter 'a' against pH are shown in Fig. 3. As the quantity of associable protons increases, the amount of free acid in the titrant decreases, and vice versa for negative values of 'a'. The total number of protons that can be dissociated from ligand molecules is indicated by positive 'a' value. Fig. 4 shows that 1 is the largest value of 'a', hence both L-leucine and isoleucine have one dissociated proton.

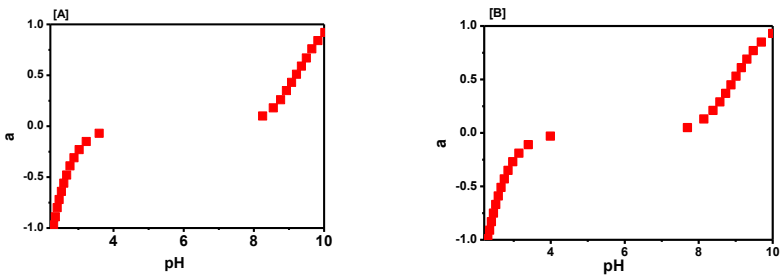

Fig. 3. Changes in value of a depending on pH in 1.0% w/v SLS concentration; [A] L-leucine [B] Isoleucine, in that order

3.2 Diagrams of the Distribution

Fig. 4 depicts normalized graphs of distributions generated by DISPLOT [33-38] using dissociation constants from the models that suit the data the best. Each system is represented by a single representative plot at a specific SLS–water concentration. Within the pH range of 4.0 to 9.0, 95% LH specie form of L-leucine is present. In the pH range of 1.8-11.0, LH_2^+, LH, and L- are present in the L-leucine distribution plot shown in Fig. 4(A). In the case of isoleucine, LH is available between pH 4.0 and 9.0 to a degree of 94%. Fig. 4(B) plot for isoleucine reveals the presence of LH_2^+, LH, and L- in the pH range of 1.9-11.2. Fig. 5 illustrates the dissociation-association equilibria of L-leucine and isoleucine.

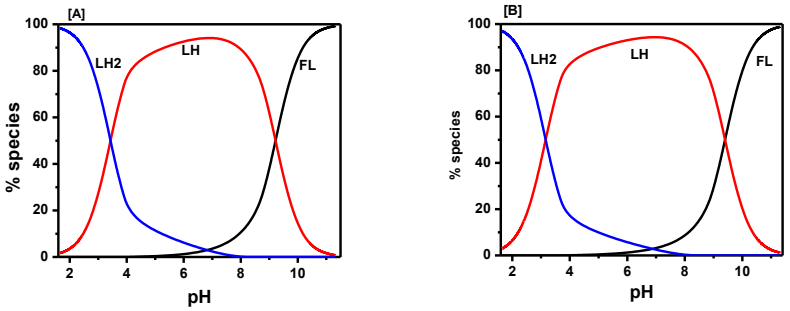

Fig. 4. Distribution schematics of [A] L-leucine [B] Isoleucine 1.5% w/v SLS concentration

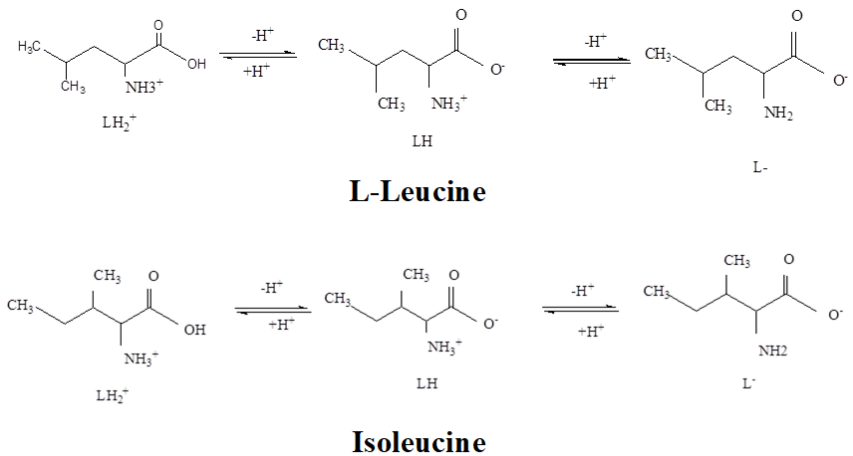

Fig. 5. Dissociation-association equilibria of L-leucine and Isoleucine

3.3 Residual Analysis [39-42]

When doing a data analysis using the method of least squares, it is reasonable to anticipate that the residuals, which are defined as the discrepancies between actual data and simulated data according to the model variables, will adhere to a Gaussian or normal distribution. If everything goes as expected, the residuals should be equal to zero once the data are fit to the models. In addition, the residuals of a model must be free of any discernible trend before it may be considered acceptable. Examining the normal distribution of residuals in a manner that is respectful of the assumption of least squares analysis. These include χ^2, skewness, kurtosis, and the R-factor. As mentioned below, these statistical parameters of the present data indicate that the best-fitting models represent the acido-basic equilibria of L-leucine and isoleucine in SLS system. Simulations using experimental titrations data using the model variables listed in Table 1.

Table 1. Accepted model of L-leucine and isoleucine acido-basic equilibria in SLS concentrations. The temperature is 303 K, and the ionic strength is 0.16 mol dm^{-3}

% w/v. SLS	Log β1(SD)	Log β2(SD)	NP	U_{corr}	Skewness	Kurtosis	χ^2	R
L-leucine (pH range 1.80 -10.50)								
0.0	9.72(6)	12.09(8)	95	76.5	-4.93	39.23	56.23	0.0491
0.5	9.49(5)	12.60(5)	77	6.16	0.73	2.88	8.18	0.0101
1.0	9.19(4)	12.70(5)	78	10.67	0.31	2.93	5.13	0.0177
1.5	9.22(2)	12.65(3)	118	58.1	1.68	6.58	48.3	0.0381
2.0	9.17(3)	12.80(7)	108	41.22	1.47	5.09	18.81	0.0364
2.5	9.20(4)	12.98(5)	81	10.01	0.94	3.78	15.58	0.0171
Isoleucine (pH range 2.00 -10.00)								
0.0	9.58(2)	11.93(3)	102	15.11	-2.44	15.15	23.53	0.0200
0.5	9.42(1)	12.36 (2)	95	9.00	1.32	6.16	18.08	0.0181
1.0	9.17(3)	12.54(5)	95	26.45	-0.38	4.12	4.44	0.0321
1.5	9.14(3)	12.56(4)	108	41.03	1.42	5.01	19.85	0.0356
2.0	9.21(14	13.16(18	93	98.3	1.04	2.72	26.39	0.0493
2.5	8.77(3)	12.34(6)	109	38.69	3.08	17.02	73.67	0.0375

3.4 Effect of Surfactant

The effect of solvent composition on these dissociation constants and associated equilibrium constants has been examined in greater depth. Log K_1 and log K_2 values for L-leucine and isoleucine were displayed as a function of the composition of SLS for this purpose. The interface of anionic surfactant SLS is negatively charged, and the anion from the acid molecule is rejected, resulting in a decrease in acidity. There is also the possibility of electrostatic attraction of H^+ from acid molecules to SLS micelles, which would increase acidity. In the present investigation, however, the combined effect of these factors has a smaller effect on the acid molecule, resulting in a smaller fluctuation in the step-wise dissociation constant values than in water.

Fig. 6 shows that a proton concentration gradient exists between the interface and the bulk solution, which accounts for the apparent discrepancy in the magnitude of dissociation constants between micellar medium and aqueous solution [43]. In addition, micelles are known to alter the dielectric constant of the medium, which in turn affects the dissociation-association equilibria [44,45]. The linear fluctuation of the log values of the stepwise dissociation constants of L-leucine and isoleucine with the composition of SLS suggests that electrostatic forces dominate the dissociation-association equilibrium.

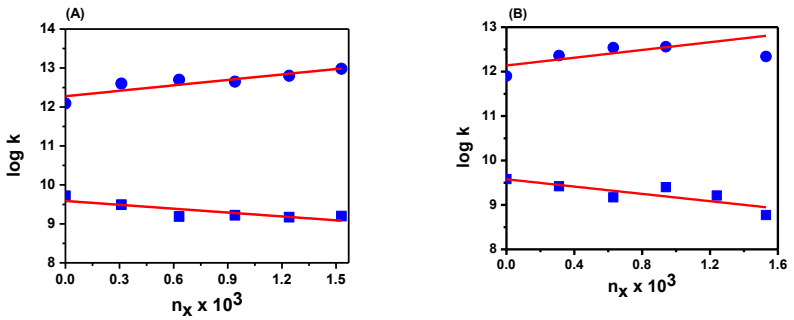

Fig. 6. Dissociation constant (log K) changes with SLS composition. [A] L-leucine [B] Isoleucine (■) logK_1 and (●) logK_2

Table 3. Errors in key factors and their potential impact on dissociation constants of L-leucine and isoleucine in 1.5% (w/v) SLS concentration

% Error	Ingredient	Log β_{mlh} (SD)			
		L-Leucine		Isoleucine	
		LH	LH_2	LH	LH_2
	0	9.22(2)	12.65(3)	9.14(3)	12.56(4)
Alkali	-5	9.66(8)	13.4(9)	9.58(7)	13.34(9)
	+5	8.3(6)	11.3(7)	8.66(7)	11.8(8)
	-2	9.40(4)	12.94(6)	9.32(4)	12.86(5)
	+2	9.04(5)	12.35(5)	8.95(4)	12.26(6)
Acid	-5	8.74(7)	11.73(9)	8.73(8)	11.77(6)
	+5	9.59(6)	13.41(7)	9.5(5)	13.34(8)
	-2	9.07(4)	12.33(7)	8.98(3)	12.24(6)
	+2	9.37(4)	12.95(5)	9.29(4)	12.87(6)
Ligand	-5	9.16(7)	12.65(9)	9.07(7)	12.56(8)
	+5	9.28(6)	12.64(6)	9.20(6)	12.55(6)
	-2	9.20(5)	12.65(4)	9.11(4)	12.56(7)
	+2	9.25(4)	12.64(5)	9.16(4)	12.56(5)

3.5 Consequences of Best-Fit Model Errors

The MINIQUAD75 cannot analyze the consequences of Best-Fit Model errors and calibration of the electrodes based on the magnitude of the protonation constant. For this test, we relied on the finest chemical model for doing analytical research and practical work over a wide range of experimental settings with varied precisions of data collection and introduced pessimistic mistakes in the quantities of base, acids, and ligands. Results from an example study are shown in Table 3; errors in alkali and mineral acid concentrations have a larger effect on dissociation constants than do ligand concentrations.

4. CONCLUSIONS

L-leucine and isoleucine both have one proton capable of dissociation and one amino group capable of forming an association with a proton. It occurs as LH_2^+ at low pH and is deprotonated with the generation of LH and L^- when the pH rises. The carboxylate and amino groups' corresponding dissociation constants are K_1 and K_2, respectively. Secondary formations, such as the number of moles of alkali consumed per mole of ligand and the average number of protons bound per mole, can identify protonation equilibria and estimate dissociation constants. The linear fluctuation of L-leucine and isoleucine dissociation constants with increasing mole percent of SLS suggests that electrostatic forces dominate in the dissociation acidio-basic equilibria. The non-electrostatic hydrophobic interactions between the solute and solvent are responsible for the non-linear component. The influence of mistakes in the relevant parameters appears to indicate that errors in concentrations of base and acids have a greater impact on dissociation constants than do concentrations of ligands. This is because errors in alkali and mineral acid concentrations are more likely to be systematic. Further research is needed to establish the potential of the specific complexes with different metal ions discovered in an equilibrium mixture at physiological pH.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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AUTHORS BIOGRAPHY

Dr. Raj Kumar Bolledula is an accomplished researcher and eminent teacher in Pharmaceutical Sciences. He is currently working as Professor at Moonray Institute of Pharmaceutical sciences, Raikal, Shadnagar, Telangana. He has completed M.Pharmacy and Ph.D. from Jawaharlal Nehru Technological University Hyderabad, Hyderabad, Telangana. He has 13years of teaching experience. He has more than 30 publications in reputed journals, one patent, an Editorial board member in national and international journals, and a reviewer for international journals. He has guided 25 M.Pharm students. He has attended many symposiums, conferences, and workshops at the national and international levels. He is a Life Member of the Association of Pharmaceutical Teachers of India (APTI) & Indian pharmacy graduate association (IPGA).

Dr. P. Sivakumar M. Pharm., Ph. D Presently working at E.R.K.College of Pharmacy, Erumiyampatti, Dharmapuri District. He completed his B.Pharm from The TN.Dr.M.G.R Medical University, Chennai, in 2005, and M.Pharm (Pharmacy practice) in 2007 from Annamalai University Chidambaram, Tamilnadu. He was awarded a Ph.D. by SunRise University, Alwar, Rajasthan, India, in 2019. He has guided 12 M.Pharm and 15 Pharm.D students. Scholars are carrying out their research projects under his supervision. He has an experience of about 14 yrs in teaching and research in pharmaceutical science. He has published 14 research papers in national and international journals.

Prof. Dr. J. Amutha Iswarya Devi, M.Pharm., Ph.D., is currently a Principal & Associate professor at St.Mariam College of Pharmacy, Pudur, Tirunelveli. Formerly she worked as an associate Professor at Arulmigu Kalasalingam College of Pharmacy, Krishnan Kovil, Srivilliputhur. Dr.J.Amutha Iswarya Devi has 19 yrs of Teaching experience in Academics and Research. She has completed B.Pharm in SBCP, Sivakasi, and M.Pharm in Pharmaceutical Chemistry at AKCP, Krishnan Kovil. Ph.D. in Pharmacy from Annamalai University, Annamalai Nagar, Chidambaram. She has published 35 research articles and 17 review articles with a Total citation of 95, a hi-index five at the National and International levels. She has h-index -5 and i-index-10 at national and international.

A. Sahithi (M.Pharm, Ph.D.) working as associate professor in Nalla Narshima Reddy Education societies group of institutions , Ghatkesar Mandal, Korremula Rd, Hyderabad, Telangana . She has completed her M.pharmacy from J.N.T.U.H.She has published 13 research articles and two review articles. She has eight years of teaching experience in Academics and Research.She has one german patent grant. She has pursuing her Ph.D. in GITAM . She is a life member of APTI.

Dr. T Venkatachalam is a professor and head department of pharmaceutical chemistry, JKKMMRF's-Annai JKK Sampoorani college of pharmacy, Komarapalayam, Namakkal DT, Tamil Nadu. He completed B.pharm in JKKMMRF college of pharmacy, M.pharm completed at Annamalai University, and was awarded a Ph.D. in pharmaceutical science from The Tamil Nadu Dr. MGR Medical University, Chennai. He has 15 years of teaching and academic research experience. He guided 15 M Pharm & 10 B . Pharm projects. He has published 49 research articles in various National & International journals, four patents & 4 Books Published. He has editorial board members & a reviewer of more than 20 national & International journals.

Unique Pub International (UPI)
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Email: info@uniquepubinternational.com

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Authors

Dr. Raj Kumar Bolledula | Dr.P. Sivakumar
Prof.Dr.J. Amutha Iswarya Devi
A. Sahithi | Dr.T. Venkatachalam

TEXTBOOK OF PHARMACEUTICAL VALIDATION

Dr. Raj Kumar Bolledula
Professor
Department of Pharmaceutical Analysis Moonray Institute of Pharmaceutical sciences Raikal, Shadnagar, R R.Dist, Telangana, India

Dr. P. Sivakumar
Professor
Department of Pharmaceutical Chemistry
E.R.K.College of Pharmacy
Erumiyampatti, Dharmapuri District, Tamil Nadu, India

Prof. Dr. J. Amutha Iswarya Devi
Principal
St.Mariam College of Pharmacy
Pudur, Tirunelveli, Tamil Nadu, India

A. Sahithi
Associate Professor
Nalla Narshima Reddy Education Societies Group of Institutions
Ghatkesar Mandal, Korremula Rd, Hyderabad, Telangana, India

Dr. T. Venkatachalam
Professor and Head Department of Pharmaceutical Chemistry
JKKMMRF's-Annai JKK Sampoorani College of Pharmacy
Komarapalayam,
Namakkal (DT), Tamil Nadu, India

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Author: Dr. Raj Kumar Bolledula
Dr. P. Sivakumar
Prof. Dr. J. Amutha Iswarya Devi
A. Sahithi
Dr. T. Venkatachalam

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Dr. Raj Kumar Bolledula
Professor
Department of Pharmaceutical Analysis Moonray Institute of Pharmaceutical sciences Raikal, Shadnagar, R R.Dist, Telangana, India

Dr. P. Sivakumar
Professor
Department of Pharmaceutical Chemistry
E.R.K.College of Pharmacy
Erumiyampatti, Dharmapuri District, Tamil Nadu, India

Prof. Dr. J. Amutha Iswarya Devi
Principal
St.Mariam College of Pharmacy
Pudur, Tirunelveli, Tamil Nadu, India

A. Sahithi
Associate Professor
Nalla Narshima Reddy Education Societies Group of Institutions
Ghatkesar Mandal, Korremula Rd, Hyderabad, Telangana, India

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Professor and Head Department of Pharmaceutical Chemistry
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Komarapalayam,
Namakkal (DT), Tamil Nadu, India

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PREFACE

The authors take a pragmatic approach and present a comprehensive interpretation of the rules that are currently in place (GMP, ICH), in addition to a discussion of the relevant calculations, parameters, and testing. Therefore, readers will be able to validate the analysis of pharmaceutical compounds using this book, all while adhering to the regulations and meeting the demands of the industry for robustness and cost effectiveness.

After providing an overview of the fundamental parameters and tests used in pharmaceutical validation, such as specificity, linearity, range, precision, accuracy, detection, and quantitation limits, the text then shifts its emphasis to a life-cycle approach to validation and the incorporation of validation into the overall analytical quality assurance system.

Analytical chemists, the pharmaceutical business, pharmacologists, quality assurance officials, and public authorities will find this reference extremely helpful due to the author's first-hand experience of the sector as well as the governing organizations.

PHARMACEUTICAL VALIDATION

THEORY

1. Introduction: Definition of Qualification and Validation, Advantage of Validation, Streamlining of Qualification & Validation process, and Validation Master Plan. Qualification: User Requirement Specification, Design Qualification, Factory Acceptance Test (FAT)/ Site Acceptance Test (SAT), Installation Qualification, Operational Qualification, Performance Qualification, Re-Qualification (Maintaining status- Calibration Preventive Maintenance, Change management), Qualification of Manufacturing Equipments, Qualification of analytical Instruments and Laboratory equipment.
2. Qualification of analytical instruments: Electronic balance, pH meter, UV-Visible spectrophotometer, FTIR, GC, HPLC, HPTLC Qualification of Glassware: Volumetric flask, pipette, Measuring cylinder, beakers, and burette.
3. Validation of Utility systems: Pharmaceutical Water System &pure steam, HVAC system, Compressed air, and nitrogen. Cleaning Validation: Cleaning Validation - Cleaning Method development, Validation, and Validation of analytical methods used in cleaning.

Cleaning of Equipment, Cleaning of Facilities. Cleaning in place (CIP).

4. Analytical method validation: General principles, Validation of analytical method as per ICH guidelines and USP. Computerized system validation: Electronic records and digital significance-21 CFR part 11 and GAMP 5.
5. General Principles of Intellectual Property: Concepts of Intellectual Property (IP), Intellectual Property Protection (IPP),Intellectual Property Rights (IPR); Economic importance, a mechanism for protection of Intellectual Property –patents, Copyright, Trademark; Factors affecting the choice of IP protection; Penalties for violation; Role of IP in the pharmaceutical industry; Global ramification and financial implications. Filing a patent application; patent application forms and guidelines. Types of patent applications: Provisional and non-provisional, PCT and convention patent applications; International patenting requirement procedures and costs; Rights and responsibilities of a patentee; Practical aspects regarding maintaining a Patent file; Patent infringement meaning and scope. Significance of transfer technology (TOT), IP, and ethics-positive and negative aspects of IPP; Societal responsibility, avoiding unethical practices.

CONTENTS

UNIT -1
VALIDATION

'Establishing documented evidence provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.'

Qualification is defined as the "action of proving that any equipment works correctly and leads to the expected results." Qualification is also part of the Validation and is product-specific.

Qualification is often a part (the initial Stage) of Validation, but the individual qualification steps alone do not constitute process validation.

There are four stages of Qualification:

- Design qualification (DQ);
- Installation qualification (IQ);
- Operational Qualification (OQ); and
- Performance qualification (PQ).

Relationship between Validation and Qualification, Validation and Qualification are essential components of the same concept. The term qualification is usually used for equipment, utilities, and systems.

Types of Validation

Process validation or simply called Validation, may be conducted at different points during the life cycle of a product. The types of process validation are defined in terms of when they occur with product design, transfer to production, and release of the product for distribution.

i. Prospective Validation
ii. Concurrent Validation
iii. Retrospective Validation
iv. Revalidation

i. Prospective Validation

Prospective Validation is conducted before a new product is released for distribution or, where the revisions may affect the product's characteristics before a product made under a revised the manufacturing process is released for distribution.

Criteria for Performing the Prospective Validation

Facilities and equipment should meet GMPs requirements Personnel has to be trained properly Critical processing steps and processing variables should be identified, and provisional operational control limits for each critical test parameter should be provided using pilot
laboratory batches (10 x)

Points to be Considered

- Different lots of raw materials should be used.
- Batches should be run in succession on different days
- Batches should be manufactured in equipment and other facilities for commercial production.
- Critical process variables should be set within their upper and lower limits during operation.
- Failure should be subjected to process requalification and subsequent revalidation if the failure occurs.

ii. Concurrent Validation

Concurrent Validation is used for establishing documented evidence that a facility and processes do what they purport to do, based on information generated during

actual imputation of the process. Concurrent Validation is a subset of prospective Validation and is conducted with the intention of ultimately distributing products manufactured during the validation study.

In-process tests that can be monitored in solid and liquid dosage forms are:

1. Powder-blend uniformity
2. Moisture content
3. Particle/granule size distribution
4. Weight variation
5. Content uniformity
6. Disintegration time / dissolution time
7. Tablet hardness
8. pH value
9. Colour/clarity
10. Viscosity/density

Selection of the in-process test process parameters should be based on the critical processing variables to be evaluated.

iii. Retrospective Validation

Retrospective validation is the Validation of a process based on accumulated historical production, testing, control, and other information for a product already in production and distribution. This type of validation uses historical data and information found in batch records, production log books, lot records, control charts, test and inspection results, customer complaints or lack of complaints, field failure reports, service reports, and audit reports.

Retrospective Validation-Method

1. Collect commercial values of in-process data and end-product testing results.
2. Organize these data in chronological order.

3. Include data from at least 20-30 batches for analysis.
4. Isolate critical processing steps data.
5. Subject the data to statistical analysis and evaluation.
6. Conclude the state of control of the manufacturing process
7. Issue a report of findings.

iv. Revalidation

Repeated Validation of an approved process to ensure continued compliance with established requirements. Revalidation should be performed following a change that couldaffect the process, procedure, quality of the product, and product characteristics. Revalidation should be performed following a change that could affect the process,procedure, quality of the product, and product characteristics.

Advantages of Validation

1. Process parameters and controls are determined during the Validation of any process or system.
2. It helps to determine the worst-case risks that may arise while manufacturingthe quality products.
3. Validation helps to investigate the deviations caused during the process.
4. Deep study and understanding of the system and equipment are made possible due to the Validation.
5. The risk of regulatory non-compliance is minimized after the Validation.
6. A validated process requires less process control and the finished product testing.
7. Batch to batch variation is minimized due to the Validation of processes, systems, and equipment.
8. Reduces the production cost of the product.

9. Increases the production of manufacturing facility due to the minimized rework and
10. rejection.
11. Decreases the chances of the failure of the batches.

Streamlining of Qualification and Validation Process
Approach to Process Validation

In all stages of the product lifecycle, good project management and archiving that capture scientific knowledge will make the process validation program more effective and efficient. Process validation involves a series of activities taking place over the lifecycle of the product and process.

Stage 1 – Process Design
Stage 2 – Process Qualification
Stage 3 – Continued Process Verification

Stage 1 – Process Design

Process design defines the commercial manufacturing process that will be reflected in planned master production and control records. This Stage aims to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes.

Stage 2 – Process Qualification

During the process qualification (PQ) stage of process validation, the process design is evaluated to determine if it is capable of reproducible commercial manufacture. This Stage has two elements:

1. Design of the facility and Qualification of the equipment and utilities and
2. Process performance qualification (PPQ).

During Stage 2, CGMP-complaint procedures must be followed. Successful completion of the Stage is necessary

before commercial distribution. Products manufactured during this Stage, if acceptable, can be released for distribution.

Stage 3 – Continued Process Verification

The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture.

An ongoing program to collect and analyze product and process datarelated to product quality must be established. The data collected should include relevant process trends and the quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and reviewed by trained personnel. The information collected should verifythat the quality attributes are being appropriately controlled throughout the process.

Qualification and Validation Protocols

As a minimum, the protocols should include the following significant background information:

- the objectives of the study
- the site of the study
- the responsible personnel
- description of SOPs to be followed
- equipment to be used; standards and criteria for the relevant products and processes
- the type of Validation
- the processes and parameters
- sampling, testing, and monitoring requirements
- predetermined acceptance criteria for concluding.

There should be a description of how the results will be analyzed.

The protocol should be approved before use. Any changes to a protocol should be approved beforethe implementation of the change.

Steps in Validating a Process

1. Develop validation protocol
2. Conduct installation qualification
3. Conduct operational Qualification
4. Conduct performance qualification
5. Analyze results and reach conclusions
6. Monitor and control process
7. Purpose: To ensure the process remains within established parameters under anticipated
1. conditions
8. Investigate deviations from established parameters
9. Take corrective action
10. Consider whether revalidation is necessary.
11. Changes in process or product.

Qualification and Validation Reports

1. Reports should reflect the protocols followed and include at least:

- the title and objective of the study
- reference to the protocol
- details of material, equipment, programs, and cycles used
- procedures and test methods.

2. The results should be evaluated, analyzed, and compared against the pre-determined acceptance criteria. The results should meet the acceptance criteria; deviations and out-of-limit results should be investigated. If these deviations are accepted, this

should be justified where necessary further studies should be performed.

3. The departments responsible for the qualification and validation work should approve the completed report.
4. The report's conclusion should state whether or not the outcome of Qualification and Validation outcome was considered successful.
5. The quality assurance department should approve the report after the final review. The criteria for approval should be in accordance with the company's quality assurance system.
6. Any deviations found during the validation process should be acted upon and documentedas such. Corrective actions may be required.

Validation Master Plan

The VMP (Validation Master Plan) serves as the validation roadmap, setting the course, justifying the strategy, outlining the preliminary test and acceptance criteria, and documenting the necessary programs to ensure a continuing Validation state.

1. Introduction

This section should include the company name, location, division or subsidiary name (if applicable) and business sector served. A short overview of the project provides the reader with the necessary background from a macro standpoint. A cross-reference to the relevant company Quality Assurance Policy is appropriate here.

2. Scope

This section defines the breadth and reach of the validation effort covered by the VMP. A brief description of

the installation, whether single- or multi-product, and a breakdown of installed equipment as new or existing should be included here.

3. Facility Description

The facility characteristics are listed here, whether the project is a new building, extension, or remodeling of a current building. The number of floors, the inter-connectivity of process and utility systems, isolation means, and the design product and personnel flow used to minimize cross-contamination are identified. Be sure to note any room classification (cleanroom certification levels), specialty surfaces, and finishes integral to achieving the required product quality.Process Flow Diagrams (PFDs) are useful here, depicting the anticipated personnel, raw material, process, and waste material flow. The emphasis here is on design considerations to eliminate cross-contamination of material.

4. Commissioning

The selection criteria governing what equipment and utility systems will undergo Commissioning are documented here. As Commissioning is not part of the Validation Program and is not regulated by the FDA, people often wonder why they should include this section. The reason is the FDA is just as interested in the rationale behind why one system is not validated while another is. The VMP needs to answer that question, identifying support utilities that do not need to be validated because they do not directly affect product quality. It also demonstrates thoroughness, showing the FDA that all systems have been examined for product quality impact. To maximize the usefulness of commissioning, the system should

be tested within the anticipated operating range of the respective OQ.

5. Qualification

The selection criteria governing what equipment and utility systems will undergo Qualification arediscussed here. Individual definitions of IQ, OQ, and PQ may be included. Company policies, regulatory references, and published guidelines should be addressed in this selection process. This discussion may include considerations such as product contacting surfaces, critical/noncritical instrumentation, direct and indirect systems, and downstream processing, among others. A discussion of protocol and final report formats may be included here, with either a reference to existing protocol development procedures or a description of the format to be utilized. Final Reports may be generated as attachments to the protocols or as separate documents.

6. Process Validation

This section addresses the selection criteria governing what equipment and utility systems mustundergo Process Validation. Company policies, regulatory references, and published guidelines should be addressed in the selection process. One such criteria is if the "results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated….". Also included is a discussion on the appropriate Cleaning Validations (CV) required to verify inter-and intra-campaign cleaning methods. Packaging and Sterility Validation needs to be addressed if this is to be a finished product.

7. Computer System Validation

A separate section should be devoted to the discussion of Computer Validation, whether in the form of a Programmable Logic Controller (PLC) or a Distributed Control System (DCS). Computer Validation criteria should also be discussed, and whether the installed control system is 21 CFR 11 compliant, i.e., secure audit trails, authority checks, etc.

8. List of Required Protocols and Procedures

Include a tabular representation of the equipment and utility systems and the required protocols and procedures associated with each. This is the essence of the VMP because it defines the validation requirements for the project and can be used to determine resource loading. This table can subsequently be used as a "Deliverables List" if the validation effort is contracted outside the organization.

9. List of Required Standard Operating Procedures (SOPs)

This should take the form of a tabular representation of the installed equipment and utility systems and the required SOP associated with each, similar to the List of Required Protocols and Procedures. This will help identify the level of SOP generation necessary to complete validation activities. These will generally be Operation, Maintenance, and Cleaning SOPs.

10. Equipment and Utility System Descriptions

An overview of the particular system should be given, aligned with the Basis of Design documentation. A listing of proposed Qualification tests (IQ/OQ/PQ) should be identified with a brief description of the procedure and how the associated Acceptance Criteria will be determined. As the VMP should be developed early in the planning stage, many

system specifics will be in the draft phase and subject to change. To avoid duplication of effort and unnecessary revisions, do not assign numeric-specific Acceptance Criteria in the VMP. Those details will be fully delineated in the following Qualification and Validation Protocols. Keep in mind the intent of the VMP as a scope and guidance document. System-specific acceptance criteria fall under the auspices of the individual protocols.

11. Additional cGMP Programs

The VMP is meant to be a Validation Life Cycle document. It should cover the activities and requirements from project inception to testing completion through a continuous monitoring and evaluation program. Associated with this effort are Quality Assurance/Quality Control procedures meant to support and update the validation effort. These programs include, but are not limited to:

- Document/Change Control
- Standard Operating Procedures
- Calibration
- Revalidation
- Operator Training

12. References

All company policies and procedures, applicable local, state, and federal regulations, and industry standards should be listed.

Qualification

User requirement specification

User Requirement Specification (URS) is a list of buyer requirements regarding the equipment to be purchased. First,

the equipment user department prepares URS. Then, it is sent to the equipment manufacturer to make it as desired criteria.

The following points should be included in a pharmaceutical user requirement specification:

1. Introduction

A brief introduction to the equipment should be written.

2. Overview

i. Intended Use: Write the use of the equipment in the manufacturing.
ii. Capacity: Write the required capacity if the equipment is in the liter or kgs.
iii. Space Availability: Write the available space for equipment installation,including height, width, and height in mm.
iv. Accuracy of Instrument: Write the desired accuracy of the instrument in decimal places if applicable.
v. Cleaning Requirements: The instrument should be easy to clean. Write if there is any specific cleaning requirement.
vi. Equipment Specific Requirements: for example, required quality of Stainless Steel (SS) as SS-308, SS-316, or SS-316L if applicable.

3. Operational Requirements

i. Functional Requirements: Specify all technical requirements for the equipment.
ii. Operation: Write the operational requirements.
iii. Control System: Specify ON, OFF, or other specific equipment control requirements.
iv. Power: Write the requirements on a power failure as autostart or manual.

v. Safety: Write the requirements of safety guard and MCB trips on short circuit or overload
vi. Environment: Temperature and humidity of the area where the equipment will be installed.
vii. Other Requirements: Write the other requirements as the metal of construction (MOC) of non-contact parts and specific requirements of seals and tubing.

4. Compatibility and Support

i. Utilities: Available power supply on which instrument shall be operated. The uninterrupted power supply (UPS) and other specific utility requirements are required.
ii. Availability: Continuous equipment operating time in hours or working shifts.
iii. Supporting Documents: Requirements of operating manual, circuit diagrams, warranty letter, change part list, spare part list, etc.

5. Abbreviations

List all abbreviations used in this user requirement specification document.

6. References

7. Approval

Factory Acceptance Test (FAT):

Factory Acceptance Test (FAT) is done at the equipment manufacturing site of the vendor before the shipping. Therefore, a proper FAT can help minimize the problems occurring during the equipment installation at the site.

A FAT protocol can be written as follows.

1. Purpose: Write the purpose of the FAT protocol as "to ensure that the equipment is designed as per the specification" and " to check the basic performance of the equipment."
2. Scope: Write the scope of this protocol as "this protocolapplies to the equipment manufactured by ABC Ltd."
3. Procedure:
   - Write the complete procedure to carry out the Factory Acceptance Test.
   - Write the procedure to check the operation of the equipment.
   - Write the action to be taken when any deviation is observed.
   - List of documents to be checked.
4. Documentation: Write the instructions for the documentation to be done during the Factory Acceptance Test.
5. Acceptance Criteria: Equipment and accessories should be according to the purchaseorder. Equipment should be as per the pre-designed parameters.
6. Verification Sheet: Include all tests and parameters that should be verified during the factory acceptance test.
   - Make: Write the make of the equipment.
   - Model: Write the model of the equipment here.
   - Capacity: Write the required capacity of the equipment.
   - Design:
     - ✓ Parts of the equipment and their design & specification.

- ✓ Write the material of construction (MOC) of all parts as SS-308 or SS-316
- Include the quantity and other details of the specific parts of theequipment.
- Control Panel: Write the quantity and specific requirements to be included in the controlpanel like auto or manual, emergency stop, etc.
- PLC: Write the PLC panel's make, model, and quantity.
- Temperature sensors: Write the type, make, model, and quantity of the temperaturesensors.
- RH sensors: Write the make, model, and quantity of the RH sensors.
- Safety Features: Write the type of emergency stop, guards on moving andelectric parts, etc.
- Documents: A list of required documents like MOC certificates, manuals, calibration certificates, warranty cards, etc.

7. Observed deviations: Write the deviations observed during this verification, their investigation, corrective action, and if those are acceptable or not.
8. Approval

Site Acceptance Test (SAT):

Site Acceptance Test can determine whether or not systems are meeting the desired and required specifications. The main purpose of site acceptance testing is to give an overall evaluation of the compliance of a system and to ensure this compliance meets the requirements of the business involved.

Site acceptance tests are related to factory acceptance tests in that they work by inspection and dynamic forms of testing to system components. The SAT (site acceptance tests) are

written by the client, and this verifies the functionality of the equipment being tested. They are also, as their title suggests, tested on-site. The test will show whether the equipment meets, does not meet, or exceeds the performance expectation.

The factory acceptance tests (FAT) are inspections that use the same principle, focuson whether the user requirements meet specifications, and are executed by the client andthe client representative. They take the manufacturer and the user into account and are tested at the factory/place of manufacturing, as their title suggests.

These tests are common knowledge in the biotech, medical, and pharmaceutical fields. Site acceptance test documents must be completed routinely for systems to meet GMP requirements. Without the SAT tests, it is difficult to see if these requirements are successfullycomplied with.

The SAT is a test of not only efficiency but quality. It is up to senior management and committed staff to keep track of system software levels across different departments. By conducting an SAT, quality assurance is met, along with good manufacturing practice, safe quality risk management, and efficient quality control checks.

Various elements of a Site Acceptance Test will be included in the test to ensure its success. These include: Finishing visual checks, main components visual checks, internal box pressure, and ventilation setting checks, the functionality of utilities to be checked, the interlocks to be checked in relation to functionality, a hot test for dispensing systems, calibrator verifications, safety devices checks and tests of the operator's training and ability.

Design Qualification

Documented evidence that the premises, supporting systems, utilities, equipment, and processes have been designed in accordance with the requirements of GMP

Design qualification should provide documented evidence that the design specifications were met.

DQ should ensure that instruments have all the necessary functions and performance to enable them to be successfully implemented for the intended application and meet business requirements.

While IQ, OQ, and PQ are performed in most regulated laboratories, DQ is not so well known to many laboratories. It is rarely performed officially in those cases where the equipment is planned for use in multiple applications, not in a specific one.

DQ is performed in most laboratories but is not called DQ. However, annexing officially requires the EU Guide for Good Manufacturing Practices DQ. Therefore inspectors from Europe and other PIC/S member countries are quite familiar with the term and may ask for DQ documents. Likewise, an FDA inspector may ask for documented user requirements.

Installation Qualification

Installation qualification establishes that the instrument is delivered as designed and specified,that it is properly installed in the selected environment, and that this environment is suitable for the operation and use of the instrument.

Installation qualification should provide documented evidence that the installation was complete and satisfactory.

The purchase specifications, drawings, manuals, spare parts lists, and vendor details should be verified during installation qualification.

Control and measuring devices should be calibrated.
The main purposes of IQ are to ensure that the

- equipment has been received as purchased,
- the equipment meets the physical hardware specification,
- the selected environment meets the vendor's environmental specifications,
- individual hardware modules and all accessories are properly installed and connected,
- the software is completely installed on the designated storage device,
- computer systems are properly configured for the intended use,
- the instrument functions in the selected environment, and
- all equipment hardware and software are registered in a laboratory equipment database.

Protocol:

1. Develop an operating procedure for IQ.
2. Generate a database for equipment.
3. Ask the vendor to perform IQ as part of the installation.
4. Correct installation of software should be verified for computer systems. Develop an installation verification master file.
5. An installation check with known chemical standards should be performed for complex modular systems.
6. Document IQ. If the vendor did IQ, the IQ document should also be signed by the vendor and user.

Operational Qualification

Operational Qualification demonstrates that an instrument will function according to its operational specification in the selected environment.

OQ should be carried out after initial installation,instrument repair,and other significantevents, such as upgrades, and at regular intervals during routine use.

OQ is an important part of the overall equipment qualification process. The careful selection of test items, the test procedures, and acceptance limits is extremely important because if set too stringently, the instrument's test may have an unnecessarily high failure rate, and the maintenance efforts will be too intense. On the other hand, if the limits are too relaxed, the equipment will not prove itself fit for its purpose.

The general procedure to qualify an instrument for operation is as follows:

1. Define the intended use and the functional and operational specifications (use criteriaas defined during DQ).
2. Develop test procedures and protocols.
3. Define acceptance criteria.
4. Perform the tests.
5. Check if test results meet acceptance criteria
6. Document the results.
7. Develop criteria and steps for requalification, e.g., after repair.
8. Develop procedures in case the equipment does not perform to specifications.

Performance Qualification

Performance qualification (PQ) demonstratesthat an instrument consistently performs according to a specification appropriate for its routine use.

Ongoing activities may include the following:

1. Preventive instrument maintenance
2. Regular calibration
3. Full or partial OQ checks
4. Daily check of critical performance characteristics, for example, baseline noise of a UV detector if the limit of detection is critical
5. Daily system suitability testing
6. Analysis of blanks
7. Duplicate analysis
8. Analysis of QC samples
9. Procedures to detect, record, and handle errors and other unforeseen events
10. Regular security checks
11. Changes to the system in a controlled manner and controlled requalification after the change, if necessary
12. Internal audits
13. Participation in proficiency testing schemes
14. Ongoing training programs for employees.

General Procedures

1. Develop an equipment logbook.
2. Develop maintenance procedures (with the help of the vendor).
3. Develop procedures and acceptance limits for performance testing (criteria: regulations, instrument type, application, performance requirements).

Re-Qualification

Requalification means ensuring that the equipment is still in the qualified state after changing andperiodic assessment of the equipment within defined time intervals.

Strictly speaking, requalification is not mentioned in Annexure 15 of the EU guidelines to GMP, which is the guidance document for Qualification in Europe. But revalidation is described, and since Qualification is considered a subset of Validation, a requalification is also required. There is no setting of time standards.

But it should be stipulated when a periodically recurring requalification has to be carried out. These requirements should not be taken and met on a general basis but system-related and risk-based. In many cases this is every 3 to 5 years. But in the case of a fully automated system for the visual inspection of parenteral, for example, it could be scheduled already every 1 to 2 years. So it is very important that this requalification is not understood as a repetition of Qualification.

Usually, no new tests or measurements are necessary as the equipment concerned was not changed. Here, requalification is instead a review of data from the routine operation. Hence, the quality-related equipment or specification parameters are to be considered and analyzed as well as the changes in the equipment and the deviations that took place in the period considered.

An analysis of the logbook should also be part of this evaluation. Finally, the document should end with a conclusion that informs about the equipment's state: equipment still is considered to be qualified:

Yes / No.

Maintaining Status For Calibration

The quality of the products manufactured by any enterprise can directly be associated with the accuracy of the instruments producing them. If the instruments are not calibrated properly or damaged and need repair work, they

will surely affect the end products. ISO calibration lists out the general requirements for the competence of testing and calibration laboratories. All the labs must adhere to service specifications developed by the International Organization for Standardization.

It is important to remember that instruments and equipment will not always stay calibrated. At some point, the calibration level will go down and affect the final measurements andquality of the products. Therefore, the instruments and equipment must always be in excellent condition. Thus, the instruments' preventive maintenance, repair, and recalibration are performed regularly.

Variables determining how frequently instruments should be calibrated or recalibrated:

i. Manufacturers' Recommendations:

Every manufacturer mentions the ideal time frame of when you should recalibrate an instrument. Follow these instructions and specifications to the letter, and you will face minimum maintenance issues. However, it is extremely important to remember that critical measurements may call for greater frequency.

ii. Annually or Biannually:

Some instruments need to be recalibrated once or twice every year. Therefore, it depends on how often the critical measurements are taken. Additionally, the amount of damage sustained by the instruments during use also plays a role.

iii. After a Damaging Incident

If any instrument was damaged in an accident, dropped hard, or sustained an injury, you must calibrate it immediately. Events where the instruments sustain damage

usually experience a sharp impact that directly affects their readings. Check if the calibration was altered and carry out the necessary calibration procedures.

iv. As Demanded by Projects:

When you carry out specific assignments, you have to use certified and calibrated test equipment, irrespective of how big or small the project is. When assignments call for such calibration based on project requirements, you must follow it.

v. Before or After a Major Project:

Some significant projects require extremely accurate measurements. This means that the instruments must be calibrated before the project starts. However, it doesn't end there. You must calibrate all the instruments that were used after the project comes to an end. Post-project calibration will show you if the testing you conducted is reliable or not and if the correct and consistent measurements were observed throughout the project.

vi. Semiannually, Quarterly or Monthly:

Based on their use and functions, some instruments need to be calibrated frequently. Therefore, if you deal with critical measurements quite often, it would be ideal for conducting frequent and consistent calibration check-ups every month or every three to six months.

Preventive Maintenance

Preventive maintenance (PM) or preventative maintenance is regularly performed on a piece of equipment to lessen the likelihood of it failing. It is performed while the equipment is still working, so it does not break down unexpectedly. Maintenance and service-related items are often

the second-largest budget element in a laboratory after salaries and benefits. Therefore, within maintenance, preventive maintenance (PM) is a substantial portion of the budget. Traditionally, PM was an equipment maintenance philosophy based on replacing, overhauling, or remanufacturing a piece of equipment at fixed intervals, regardless of its condition. In essence, it involved fixing something that wasn't necessarily broken, and this approach is still widely used in the pharmaceutical industry.

The typical rationale for performing PM includes:

- Original equipment manufacturer (OEM) recommendations.
- Maintaining the performance specifications of an instrument.
- Meeting regulatory requirements.
- Maximizing uptime and minimizing corrective maintenance.
- Increasing the life of the instrument.
- Assuring end-user productivity and efficiency.
- Risk assessment there are two significant risks to consider when establishing a PM program:
- complying with regulatory issues and
- finding the right balance between over- and under-maintaining instruments and equipment.
- Two factors must be taken into account to ensure the PM program achieves a satisfactory level of maintenance:
- The first factor is equipment failure. If the performance degrades slowly as the parts wear, PM must be performed to keep the equipment operating within specification.

- The second consideration is to ensure that mechanical parts subject to wear are included in programs for replacement, cleaning, and lubrication. These parts are vulnerable to friction forces and need to be replaced.

The main issue with equipment regarding mechanical parts is PM frequency because the degree of wear is directly related to the usage rate. Schedules are generally based upon the maximum usage rate, so parts for equipment, not 100% utilized may be replaced long before they experience significant wear.

In an effective PM strategy for instruments and equipment where a PM program is effective, six variablesshould be evaluated as they can significantly affect the cost of the procedure:

i. labor source
ii. parts
iii. delivery methodology
iv. frequency
v. scheduling
vi. and compliant documentation and reporting.

i. The first variable to consider is the source of labor to perform the PM functions. For example, some laboratories employ full-time instrument technicians, usually the cheapest option providing sufficient work.
   A second option is to use each OEM (Original Equipment Manufacturer) to perform the work on their branded instruments, usually under an annual service contract. This is typically the most expensive option, but the scientific staff may prefer itbecause of the OEM's experience with their products and the trusting relationships cultivated with the manufacturers.

ii. PartsThe second variable to consider is the source of parts used to perform the maintenance. If the OEM provides the service, then original parts are automatically used, generally in the form of a PM kit. However, with a multivendor service provider, the client often has the option of using equivalent parts from a secondary source.
iii. DeliveryThe the third variable is the PM delivery methodology employed by the service provider. Most OEMs produce PM kits to replace every part in the kit, whether worn or not. But, again, this is the most expensive option. Multivendor direct service providers can employ an alternative solution: 'inspect and replace.' During the maintenance, the service technician inspects each part and replaces only those that have worn or degraded.
iv. FrequencyThe fourth variable is determining the frequency of PM. Many laboratories simply accept the OEM's recommendation, which may be based upon replacing the part with the lowest mean time between failure (MTBF) rate. As parts wear at different rates, some will still be well within specification. These recommendations may also be based on the maximum usage rate for the instrument, while the actual usage may be significantly below this.
v. SchedulingThe fifth variable is determining PM scheduling. This is usually not an issue for in-house or on-site service technicians, but for the other options, it can significantly increase the cost if not properly managed. Each service call may include travel expenses and minimum charges, so minimizing the number and frequency of appointments is beneficial. It is common practice to group equipment for a

particular vendor so that multiple PMs can be completed in one visit.

vi. ReportingThe sixth variable is compliant documentation and reporting.The client expects that the service provider will always generate the correct documents in the proper form to meet the standard's requirements. However, this confidence is not always warranted because the quality of these documents can vary greatly depending on the provider's expertise; thus, random internal audits of the records are always recommended.

Change Management

Change management is a systematic approach to the transition or transformation of an organization's goals, processes, or technologies. Change management aims to implement strategies for effecting change, controlling change and helping people adapt to change.

In the pharmaceutical industry, a change and deviation management system (CMS) is a central part of drug product manufacturers' overall quality management system. According to the FDA and International Conference on Harmonisation (ICH), a formal CMS should be established to evaluate all changes that could affect a pharmaceutical manufacturing company's production and control of the drug product, intermediate, or API.

FDA requirements and typical failures FDA considers change control a very critical GMP compliance issue; therefore, it has been one of the main criteria used by the agency in determining their drug inspection depth and coverage and their decision for follow-up regulatory actions (e.g., Warning Letter issuance). The FDA's strategy for drug inspection and follow-up is evidenced in their systems

inspection program introduced in 2002 for drug product inspection and in 2006 for API inspection.

Typical significant GMP deficiencies related to CMS include:

- The failure to evaluate FDA filing requirements; i.e., whether to file for priorapproval or changes being effected or to report the difference in the next annual report.
- The failure to file changes with the FDA.
- The failure to evaluate and justify whether equipment/system requalification isneeded to support an equipment/system change and whether process revalidation,stability studies, or equivalency studies are required to keep a process andprocessing parameter change.
- The preliminary review and approval of the change by the quality control unit.
- The FDA expects the intimate involvement of the quality control unit in the changecontrol review and approval process and usually holds the quality control unitresponsible for deficiencies regarding change control, which can beevidenced in several Warning Letters issued in the past years.

One example of this FDA expectation was documented in a Warning Letter issued by the FDA in 2003. A company performed a routine replacement of the filling pump pistons without filing a change request because it was a "like-to-like "replacement (which has been a typical industry practice). Although the replacement pistons had the same part number as the original pistons, they were slightly longer. This longer dimension caused the pistons to come into contact with the bottom of the filling blocks, resulting in the generation of

metal particles, which contaminatedthe product batches. This metal contamination resulted in the recall of several product batches and the FDA issuing a Warning Letter.

Implementing an effective CMS (Change Management System)-

- Quality risk management should be used to evaluate proposed changes.
- To ensure the change is technically justified, expert teams should evaluate proposed changes with the appropriate expertise and knowledge from relevant areas (e.g., pharmaceutical Development, manufacturing, quality, regulatory affairs and medical).
- After implementation, an evaluation of the change should be undertaken to confirm thechange objectives were achieved and that there was no harmful impact on productquality.
- Develop a change management tracking system to facilitate effective change control.
- Electronic-based CMS is a new paradigm for managing change in an ideal environment. This solution smoothly complies with the requirements mentioned above and provides a means of bypassing potential barriers and obstacles.

Qualification of Manufacturing Equipment
Equipment Qualification

- Equipment is a collective analytical measurement assembled to perform a mechanical process.
- Without a piece of equipment, we cannot manufacture a product.

- So, EQ (Equipment Qualification) proves that equipment works correctly and accordingly to give accurate and reliable results.
- If equipment is validated, we can ensure that our product is of the best quality.
- So term validation and Qualification are interlinked to each other.

Qualification

Qualification is proving and documenting that equipment or its ancillary system is installed correctly, works accordingly, and leads to the expected result. So, the term QUALIFICATION is categorized into four different parts as follows:

I. Design Qualification
II. Installed Qualification
III. Operational Qualification
IV. Performance Qualification**.**

Who should do Equipment Validation?

- The vendor or the user is responsible for the accuracy of the analysis results and equipment qualification.
- The user should always do DQ.
- While the user usually does IQ for a small and low-cost instrument, IQ for large,complex, and high-cost devices should be done by the vendor.
- OQ can be done by either the user or the vendor.
- The user should always do PQ because it is very application-specific, and thevendor may not be familiar with it.
- As PQ should be done daily, this limits tasks to the user.

Design Qualification (DQ)

"Design qualification (DQ) defines the functional and operational specifications of the instrument and details for the conscious decisions in the selection of the supplier."

The steps that should be considered for inclusion in a design qualification. Description of the analysis problem, Description of the intended use of the equipment, Description of the intended environment, Preliminary selection of the functional and performance specifications, Preliminary selection of the supplier, Final selection of the equipment, Final selection of the supplier, Development and documentation of final functional and operational specifications,

Installation Qualification (IQ)

"Installation qualification establishes that the instrument is received as designed and specified,that it is properly installed in the selected environment, and that this environment is suitable forthe operation and use of the instrument."

The Qualification involves the coordinated efforts of:

- The vendor.
- The operating department.
- The project team (which provides input into the purchase, installation, operation, and maintenance of the equipment).

Operational Qualification (OQ)

"Operational qualification (OQ) demonstrates that an instrument will function according to its operational specification in the selected environment." The proper

equipment operation is verified by performing the test functions specified in the protocol.

After the test functions are checked, a conclusion is drawn regarding equipment operation,and all data has been analyzed.

Following are the contents of the equipment operation qualification:

1. Application S.O.P's
2. Utilization List
3. Process Description
4. Test Instrument Utilized To Conduct Test
5. Test Instrument Calibration
6. Critical Parameters
7. Test Function (List)
8. Test Function Summaries

Performance Qualification (PQ)

"Performance Qualification (PQ) demonstrates that an instrument consistently performs according to a specification appropriate for its routine use. " Therefore, PQ should always be performed under conditions similar to systematic sample analysis.

PQ should be performed daily or whenever the equipment is being used.

PQ can mean system suitability testing, where critical key system performance characteristics are measured and compared with documented.

List of Manufacturing Equipment Used More Often

- Dry powder mixer
- FBD (Fluidised Bed Dryer)
- Tablet Compression Machine

- Autoclave
- Capsule filling machine
- Homogenizer

Dry Powder Mixer

Mixing an excipient and API dry ingredient is a critical step in solid dosage form preparation that significantly affects content uniformity.

Types of Powder Blender

- V cone Blender
- Double Cone Blender
- Drum mixture
- Ribbon Blender
- Conical Screw Mixer
- Tumble Blender.

URS for Powder Blender

- Operating criteria must be adequate
- Spare should be available
- Easy maintenance
- Equipment should not disseminate dust
- Low cost
- Non-reactive surfactant
- Capacity
- Mixing speed

Installation Qualification

- Detail of Equipment:
- Equipment name, made by and model no. Shall be noted down.
- The location for installation equipment shall be checked

- Utilities required shall be listed down
- Any deviation observed while following the above procedure should be informed for corrective action.

Installation Procedure

After checking all the specifications mentioned in the selection criteria, theservice engineer shall verify the equipment.

The authorized validation team shall carry out installation checks.

SR.NO	Description	Specification	Method of Evaluation	Observation
1	Equipment type		Visual inspection	
2	Surface finish		Visual inspection	
3	Driving motor		Visual inspection	
4	Gearbox		Visual inspection	
5	Control panel & button		Visual inspection	
6	Dimension		Measure tape	

Operational Qualification

- After successful installation qualification, initiate the operation to ensure that the machine is operating within specification.
- Check the operation qualification parameters against their specifications.
- Document the deviation details
- The quality and department heads shall decide whether the deviation is acceptable.

SR.NO	Description	specification	Method of Evaluation	Observation
1	On/ off Switch		Lift the on the switch and ensure that power supply is required by proper visualizing whether the drum/ cone started to rotate or not	
2	RPM (Revolution per minute)		Measure the actual RPM using a stopwatch	
3	Gross capacity		Fill the drum/cone with potable water and record	

Performance Qualification

- Load the materials to be mixed in the mixer
- Start the mixer and rotate it for the time as mentioned in the BMR.
- After completion of mixing, switch OFF the mixer and separate the drum.
- Collect the sample as per the sampling procedure.
- Send the samples to the Quality control dept. for content uniformity, bulk density, and sieve analysis

Fluid Bed Dryer

- Fluid bed drying is the most widely used technique for drying pharmaceutical powders and granulation.
- Direct contact between particles and air/gas is possible in a fluid bed system.
- Here any inert gas or air is used.
- They can be designed in either batch or continuous type fluid bed dryer

Principle

- In a fluidized bed dryer, hot air is passed at high pressure through a perforated bottom of the container containing granules to be dried.
- The granules are lifted from the bottom and suspended in the air stream.
- This condition is called a fluidized state.

FBD Design Qualification

The goal is to perform something similar to risk analysis and check a technical system's design documents to ensure that it then fulfills the user requirements.

In a fluidized bed dryer, the design of the instrument should be:

- Should occupy a small place
- Based on our requirement, we can go for horizontal or vertical.
- The bed which contains the material should be dried in a conical shape, or less some particles may retain as such at the corners
- All technical considerations should be kept in mind while doing the design.

Installation Qualification (IQ)

Installation Qualification for fluidized bed dryer includes the following steps:

- Verifying the approved purchase order.
- Check the manufacturer and supplier.
- Check for any physical damage.
- Verify that the utilities required are available.
- User manual
- Maintenance manual.
- List of charge parts.
- Electrical drawings.

Especially for FBD

- Air temperature distribution.
- Inlet air installation
- Microbiological quality of the inlet air.
- Influence of weather on inlet air conditions

Operational Qualification (OQ)

- Documented verification that the system performs as intended throughout all anticipated operating ranges; some of them include:
- Verify alarm control.
- Verify that all switches and push-button are functioning correctly.
- Heat should be distributed equally throughout the system.
- Do the tests for uniform distribution of air.
- Establish a training program for relevant stages.
- Operate all parts at their low, medium, and high levels.

Run three batches of each product and analyze for:

- Speed of air (velocity of air).
- Active ingredients homogeneity.
- Moisture content.
- Particle size distribution.
- Percentage fines.
- Tap density.

Based on this data, we can fix drying endpoints for each process.

Performance Qualification (PQ)

PQ means to check what we want for that particular process from the equipment and what processes are to be monitored.

- Inlet airspeed.
- Quality of air.
- Uniform distribution of air.
- Mixing of air with temperature.

Run the trail batch during operation, and there should not be any change in the

- Size
- Shape
- Surface characteristics.

Disintegration Apparatus

Design Qualification:

Installation Qualification

Few critical parameters during installation

Room Temperature - 15-30˚C

RH - 20-70%

Table Strength - Should have sufficient strength to place the equipment

Base/surface - Smooth and leveled steady base
Voltage - 220V ± 10 %
Earthing - Less than 3 V b/w neutral & earth

Operational Qualification

1. Number of Cycles (With a constant frequency of 29 to 32) per minute:

i. Record the frequency of moving up and down of the Basket rack assembly in a given time as shown below

Start Time (Mins.)	End Time (Mins.)	Side A (Left hand side of the operator).		Side B (Right hand side of the operator).	
		No. Of cycles (A)	No. of cycles per min. (A / 5)	No. Of cycles (B)	No. Cycles per min. (B / 5)
0	5				
15	20				
30	35				
45	50				
60	65				

ii. Record the frequency (of moving up and down) manually with respect to time.
iii. Do not stop the instrument in between the operation.
iv. Measure the frequency initially and after each fifteen-minute interval from the start, for 5 minutes each.
v. Record five readings.
vi. Divide the observed reading by five & note the frequency of moving up &down per minute.
vii. Perform the test for both the basket rack assembly positions (side A & side B) individually.

Acceptance criteria: The No. of cycles per minute should be between 29 to 32 throughout the period of operation

2**. Calibration for Temperature Maintenance**

Time (In Mins.)	Temperature (In °C)	
	Side A (Left hand side of the operator).	Side B (Right hand side of the operator).
Initial		
After 15		
After 30		
After 45		
After 60		
After 75		
After 90		
After 105		
After 120		

i. Set the temperature to 37°C.
ii. Fill the beaker with water.
iii. Attach the basket rack assembly & start the constant frequency of moving up &down.
iv. Insert the calibrated thermometer in one of the tubes of the basket rack assembly.
v. Wait till the temperature reaches between 36°C to 38°C.
vi. Start recording the readings.
vii. Record the temperature readings initially & after each 15 minutes interval up to 120 minutes from the start.
viii. Perform the test for both the basket rack assembly positions (side A & side B)individually.
ix. While performing the test, do not constantly keep the thermometer inside the basket rack assembly, but insert it 2 to 3 minutes before the measurement to give a stable reading.

Acceptance criteria: The temperature should remain within 37 ± 1°C throughout the operation.

3.Calibration of the Distance Traveled (Stroke height)

Time in mins.	Distance traveled by the basket	
	Side A (Left hand side of the operator)	Side B (Right hand side of the operator)
Initial		
After 60		
After 120		

i. Attach the basket rack assembly firmly.
ii. Attach white paper firmly without kinks on the instrument, parallel to the path of the arm of the basket rack assembly.
iii. Select one point on the horizontal arm of the assembly & mark the same on the paper (a pointed marker or pen can be used) when the assembly is not moving & at its highest position.
iv. Start the instrument by pressing the START / STOP key & followed by pressing the respective timer key.
v. As soon as assembly reaches the lowest position, mark the same point again on the paper (while doing this activity, take the time to decide the exact most downposition & then mark).
vi. Measure the distance between two marks using a calibrated ruler.
vii. Remove the paper.
viii. Perform the test initially, after 60 minutes from the start & after 120 minutes from the start.
ix. Perform the test for both the basket rack assembly positions (side A & side B) individually.

Acceptance criteria - Distance traveled is between 53 to 57mm.

Frequency- Once a Month.

Performance Qualification

Performance qualification should provide documented evidence that utilities, systems, or equipment and all its components can consistently perform in accordance with the specifications under routine use.

Test results should be collected over a suitable period to prove consistency.(Calibration)

Dissolution Apparatus

1. **Vessel Support Plate (Base plate):**
    - A spirit level may be used. Base plate inclination is less than 0.5° in two orthogonal directions. Most base plate designs allow adjustment of levelness, if necessary, usually by rotating adjusting screws on the feet of the support and frame assembly.
    - The strain of the test assembly structure from the mass of the filled water bath should be considered. Thus the levelness of the vessel support base should be confirmed with the water bath filled.
    - The condition of the vessel support plate should be visually evaluated and found to be uniform, even, and not distorted.In addition, the vessel support plate should resist deformation when under load by filled vessels.

2. Shaft Verticality

- Use a digital protractor to check the verticality of the stirring elements.
- Measure the verticality for each stirring element in two orthogonal positions.The ideal reading obtained on a vertical surface is 90.0°. Therefore, the deviation

should be less than 0.5° from 90.0° for this measurement.

3. Centering

- Measure the centering with respect to the cylindrical vessel not more than 2 cm below the vessel flange. Use the centering gauge to evaluate the alignment of the stirring element and the vessel. The difference between the most significant and smallest observed readings should not exceed 2.0 mm for 360° rotation.
- Alternatively, the centering can be measured using an inside divider to obtain a distance and the length with a vernier caliper or a micrometer. This alternative method measures the distances from the shaft to the inner vessel wall at four locations equally spaced around the vessel and no more than 2 cm below the vessel flange.The difference between the largest and smallest readings is not greater than 2.0 mm.

4. Paddle or basket height:

- The paddle or basket height can be set by placing the 25mm depth gauge.
- Checking the height with ''GO or NO-GO GUAGE.''

5. Heat Distribution

- Operate the instrument as per the respective operating procedure.
- Set the temperature by the temperature knob at 37.8°C. Start the stirrer at 50 rpm.
- Ensure that the temperature indicator is calibrated and the calibration tag is affixed.
- Note the observed temperature as shown in Annexure

- Observe the rise in temperature on the digital temperature indicator. When it shows 37°C, consider that time as "ZERO" minute.
- At this time, measure the temperature individually of all dissolution bowls by calibratingthe thermometer.
- The apparatus is satisfactory if the temperature observed for all bowls is between 36.5 °C and 37.5°C

6. Uniformity in Rotational Speed

- Operate the instruments as per the respective standard operating procedure.
- First, set the speed at 50 rpm.
- Count the rotation by Tachometer.
- Change the setting to 75 rpm, 100 rpm, and 150 rpm

7. Checking of Wobbling

- Fix the paddle/basket apparatus to the instrument, and lower the apparatus.
- Fix the wobbling meter on the top of the bowl.
- The needle of the wobbling meter should touch the surface of the apparatus.
- Measure the wobbling on the meter
- The USP limit for wobble is ±2mm

Qualification Of Analytical Instruments

1. Electronic Balance

Design Qualification:

The supplier has ISO 9001:2000 certification.

Installation Qualification

- Checking all requirements set during the instrument selection, such as electricity, humidity, temperature, etc.

- Allowing sufficient shelf space for the equipment, SOPs, operating manuals, etc.
- Comparing equipment, as received, with the purchase order, including accessories, spare parts, etc.
- Checking documentation for completeness like operating manuals, maintenance instructions, health and safety instructions, etc.
- Checking equipment for any damage.
- Reading the supplier's safety instructions, if there are any.
- Installing hardware following the manufacturer's recommendation.
- Switching on the electronic balance and ensuring all the modules power up.
- Preparing an installation report

Operational Qualification

Test procedure	Acceptance limits	Test frequency	Remarks
1.Measurement of reference weight by using 10mg ,50mg ,100mg ,500mg ,1g ,5g,10g, &20g 2.Comparing the actual results with reference weights	0.1%	Daily or when used, whatever is longer with internal reference weights Yearly with traceable external weights through instrument	The external standard should be traceable to national standard

		vendor	

Performance Qualification

- Defining weights and weight classes to be used.
- Defining acceptance limits of results.
- Defining test intervals.
- Defining corrective actions on what to do if the electronic balance does not meet the criteria. In other words, if the results are out of specification

2. pH Meter

Design Qualification

- Selection of a manufacturer that can satisfy the needs of the laboratory.
- Should have ISO 9001 certification.

Installation Qualification

- Checking all requirements set during the instrument selection, such as electricity, humidity, temperature, etc.
- Allowing sufficient shelf space for the equipment, SOPs, operating manuals, etc.
- Comparing equipment, as received, with the purchase order, including accessories, spare parts, etc.
- Checking documentation for completeness like operating manuals, maintenance instructions, health and safety instructions, etc.
- Checking equipment for any damage.
- Reading the supplier's safety instructions, if there are any**.**
- Installing hardware following the manufacturer's recommendation.

- Switching on the pH meter and ensuring that all the modules power up.
- Preparing an installation report.

Operational Qualification

Performance Qualification

A logbook is prepared for operators and service technicians to record all equipment-related activities in chronological order

Parameter to be checked	Typical frequency	Typical tolerance limit
Slope	Each day of use or before each series of measurements	95.0 to 105.0%
Offset (pH asymmetry)		+/-30mV (offset of manufacturer +/-0.5 pH units at defined temperature)
Reference buffer solution		+/-0.05 pH units

3. UV-Visible Spectrophotometer

Design qualifications

Feature	Consideration
Instrument set-up and control	• Pc based or integrated system. • Software control of operating conditions and parameters. • Data acquisition, processing and presentation needs. • In-built diagnostic facilities. • Self-testing diagnostics. • Detector options. • Source options.
Sample introduction and throughput	• Sample throughput, presentation and introduction needs. • Sample thermostating requirements. • Sample volume requirements.
Materials of construction	Resistance to corrosion, contaminated by solvents and sample.

Feature	Consideration
Installation requirements	• Size and weight in shipped form. • Access restrictions to permanent site.
Operational requirements	• Limitations on, requirements for and expected consumption of services, utilities, and consumables (*e.g.* lamps). • Ventilation requirements. • Controlling software embedded or separate package.
Environmental conditions	• Environmental conditions within which, or range over which, the instrument is required to work within specification. • Recyclability of instrument.
Maintenance and support	• Ease of user maintenance and cleaning. • Cost, longevity and availability of spares and parts. • Cost and availability of service contacts and technical support. • Suggested intervals between and procedures for maintenance and calibration of the instrument. • The period for which support (qualification, maintenance, parts, etc.) for the instrument can be guaranteed.
Training requirements	The level of skill required to operate the instrument and details of any training necessary and courses provided by the supplier.
Accessories	Desired adaptation of the system
Documentation	• Clarity and ease of use of documentation (*e.g.* operating manuals, qualification protocols, model SOPs). • Manuals available as separate hardcopies or computer files (*e.g.* on CD ROM), or held as digitally embedded copies within the instrument. • Unique document identification by version number and date of issue.
Health and safety	• Health and safety and environmental issues and /or requirements. • Significant generation of ozone.

Feature	Consideration
Photometric drift	Stability of the measurement over time, making comparisons meaningful.
Stray light	Affects accuracy and linearity
Data collection	• Expression of data on % absorption or % transmission scales. • Single or repeat scan facility. • Single or multiple wavelength monitoring. • Full spectra data (*e.g.* diode array).
Data manipulation	• Spectra subtraction. • Spectral derivatives. • Audit trail facility. • Is raw data uncorruptable ? • Back-up and restore capabilities.
Data storage	• No storage. • Embedded memory. • File transmission to external device. • Stored output via optical or magnetic media. • System security.
Data output	• Inbuilt hardcopy output-data only, spectrum only, data+ spectrum. • PC based data processing. • Custom report generation.

Installation Qualification

- The instrument has been delivered as ordered, e.g., according to the DQ or purchase order.
- The instrument has been checked and verified as undamaged.
- The appropriate documentation has been supplied, and it is of the correct issue and uniquely identified by part number, version number, and date.

- Details of recommended service and calibration intervals (carried out by the supplier) have been provided.
- Intervals, methods, and instructions for usermaintenance and calibration have been provided, along with contact points for service and spare parts.
- The correct hardware, firmware, and software have been supplied, and it is of correct tissue and uniquely identified by part number.
- Information has been provided on consumables required during the regular operation of the instrument.
- The selected environment for the instrument system is suitable, with adequate room for unpacking, installation, operation, and servicing, and appropriate services and utilities have been provided.
- Health, safety, and environmental information relating to the operation of the instrument has been provided, and the proposed working environment is consistent with these requirements.
- The response of the instrument to the initial application of power is as expected and checked for any deviations

Operational Qualification
Wavelength Accuracy- Holmium Oxide Solution

Test procedure	Acceptance limits	Test frequency	Remarks
Wavelength maxima of holmium oxide solution is measured at 241, 287, 361 and 536 nm.	• ±1 nm in UV range • ±3 nm in visible range	Six months	Standard is traceable to national standard.
Wavelength accuracy- holmium oxide filter			
Test procedure	Acceptance limits	Test frequency	Remarks
Wavelength maxima of holmium oxide filter is measured at 361, 418 and 536 nm.	• ±1 nm in UV range • ±3 nm in visible range	Six months	Filter is traceable to national standard.

Absorption Intensity

Test procedure	Acceptance limits			Test frequency	Remarks
	wavelength	A 1%/1cm	Limits		
Absorption of potassium chromate solution is measured.	• 235 (min) • 257 (max) • 313 (min) • 350 (max)	• 124.5 • 144.0 • 48.6 • 106.6	• 122.9-126.2 • 142.4-145.7 • 47.0-50.3 • 104.9-108.2	Six months	Standard is traceable to national standard.

Stray light

Test procedure	Acceptance limits	Test frequency	Remarks
Absorption of 1.2% potassium chloride solution at 200 nm is measured against water.	Absorption at 200 nm >2.0 AU	Six months	Alternative standards: • Sodium nitrite • Sodium iodide.

Control of cuvette

Test procedure	Acceptance limits	Test frequency	Remarks
Transmission of cuvette (water) against air.	a) Quartz cuvettes: • 85% at 220 nm • 88% at 240 nm b) Glass cuvettes: • 85% at 356 nm • 88% at 650 nm	Six months	Standard is traceable to national standard.

Wavelength Resolution

Test procedure	Acceptance limits	Test frequency
Spectrum of toluene is measured from 260 to 275 nm. Ratio of peak height to valley is calculated.	Absorbance ratio peak to valley at 266/269 nm > 1.5	Six months

PERFORMANCE QUALIFICATION:

Parameter	Reason	Procedure
Wavelength calibration	Critical to accuracy of results.	Can be determined using only two calibration wavelengths, preferably bracketing the analytical wavelength.
Photometric accuracy	Critical to accuracy of results	Can be determined for particular absorbance at particular wavelengths using calibrated filters or cuvettes filled with standard solutions.
Linearity of photometric response	Critical to accuracy of results	Can be determined by checking the accuracy of a number of normal absorbances across the desired absorbance range. Extrapolation beyond highest standard is inadvisable.
Signal to noise ratio	Important for sensitivity and limit detection	Can be determined from the response of a detector to a dilute standard solution and/or a blank.
Stray light	Important measure of 'health' of whole system	Record uncorrected spectrum in single beam mode for double beam instruments or with baseline correction switched off for single beam instruments.

4. Gas Chromatography (GC)

Design Qualification

- Supplier must provide documented evidence that the product has been designed, developed, and manufactured in a quality environment, e.g., ISO 9001:2000 certification.
- Supplier must provide phone and on-site support in case of defects.
- Supplier must provide information on the availability of new firmware upgrades through the internet.

Installation Qualification

- Equipment is compared as received with the purchase order, including software, accessories, spare parts, and consumables.
- Documentation checked for completeness of operating, maintenance instructions, standard operating procedures for testing and safety, validation certificates and health and safety instruments.
- Equipment is checked for any damage.
- The supplier's instruction for installation is read.
- The supplier's safety instructions are read, if there are any.
- Hardware (computer, equipment, fittings, and tubings for fluid connections, power cables, data flow, and instrument control cables) is installed following the manufacturer's recommendation.
- The instruments are switched on, all modules power-up, and an electronic self-test is performed. Any deviations are recorded.
- Software is installed on the computer following the manufacturer's recommendation.
- Correct software installation is verified.
- A backup copy of the software is made.
- Peripherals, e.g., printers and equipment modules, are configured.

Operational Qualification

Precision of peak retention times

Test procedure	Acceptance limits	Test frequency
• Five injections of a standard. • Calculation of relative standard deviation.	<1% RSD (Relative Standard Deviation)	Yearly

Precision of peak areas

Test procedure	Acceptance limits	Test frequency
• Five injections of a standard. • Calculation of relative standard deviation.	<2% RSD	Yearly

Accuracy of the temperature of the column oven

Test procedure	Acceptance limits	Test frequency	Remarks
Temperature in column oven is measured and compared with setpoint.	±1°C	Yearly	The temperature measurement device should be calibrated and traceable to a national standard.

Precision of heated zone temperature

Test procedure	Acceptance limits	Test frequency	Remarks
Actual temperature is measured and compared with setpoints at 50,70 and 90°C	2°C	Yearly	The temperature measurement device should be calibrated and traceable to a national standard.

Precision of Injection

Test procedure	Acceptance limits	Test frequency
Blank solvent is injected after standard. Peak ratio is measured between blank and standard injection.	<5%	Yearly

Carryover of Injection

Test procedure	Acceptance limits	Test frequency
• Five injections of a standard. • Calculation of relative standard deviation.	<2% RSD	Yearly

Flow Rate Accuracy

- The digital flow meter is connected to the detector outlet port.
- The carrier gas flow is set, and wait till it reaches the set flow.
- The observed flow in replicate is noted.
- The procedure is repeated for other carrier gases such as hydrogen and air.

- The flow rate of carrier gas should be ±10% of the set flow

System Precision

- 20ml of methanol, ethanol, and acetone is transferred into a 100ml volumetric flask made up of ethyl acetate.
- Blank is injected, followed by standard preparation in six replicates.
- The areas and retention times are noted down.
- The %RSD (Relative standard deviation) of retention time should not be more than 1.0%, and peak area NMT (not more than) 5.0%

Detector Noise and Drift Test

- After GC is ready, the system is run for up to 15 minutes through the single run.
- When the run is completed,the software calculates noise and drift.
- The acceptance values are:
  a) Noise not more than 100µV.
  b) Drift not more than 2500µV/hr.

UNIT -2
2A QUALIFICATION OF ANALYTICAL INSTRUMENTS

Validation of an analytical procedure is the process by which it is established, by laboratory studies, that the performance characteristics of the procedure meet the requirements for the intended analytical applications." (Definition of Validation: USP)

Qualification is part of the validation, but the individual qualification steps alone do not constitute process validation Qualification deals with components or elements of a process.Validation deals with the entire manufacturing process of a product

2.1 Calibration of Electronic Balance

Many types of balances are used in chemical and biological tests.

These balances must be calibrated to ensure the accuracy of the data produced by them. Different types of balances used are as follows:

Type	Ordinary name	Number of digits after decimal position (g)	Accuracy Class
1.	Ultra Micro Balances	7	I
2.	Micro Balances	6	I
3.	Semi-micro Balances	5	I
4.	Analytical Balances	4	I
5.	Precision Balances	1 to 3	II
6.	Technical Balances	0 to 1	III

Requirements of the balance

It should work under optimal conditions like weighing room, weighing bench, temperature, light, air,etc

S.NO	REQUIREMENTS	ACCEPTANCE
1	Weighing bench	It should be non-magnetic, vibration-proof & dust-free
2	Temperature	The constant temperature should be maintained. Deviations should not exceed 5°c
3	Atmospheric humidity	It should be between 40% to 60%
4	Light	It should be protected from direct sunlight
5	Weighing vessel	The smallest possible weighing vessel was used. Weighing vessel and sample it contains should have the same temperature

2.2 Calibration of pH Meter

Two-point calibration method

This is the method in which the pH meter is calibrated with two different buffers of known pH and then checked the pH meter against the pH 7.00 standard buffer to confirm the calibration.

Again place the tip of the electrode in the second calibration buffer, i.e., either in pH 4.00 or 10.00, and repeat the procedure.

Procedure

- Check the level of the 3M KCL electrode filling solution(electrical conductor between reference &sample) to ensure that it is within 25mm of the filling hole(small circular hole on the side of the electrode).
- Then rinse the probe with de-ionized water & blot dry with wipes & then place the tip of the electrode into the pH 7.00 buffer solution and pH 4.01 buffer or pH 9.20 buffer
- The pH meter will automatically read the endpoint when the reading is stable &an appropriate buffer symbol will appear on display and record the pH value
- Note the endpoint when the reading is stable, and an appropriatebuffer symbol will appear on display.
- The pH meter will also display the electrode slope value. Refer to the troubleshooting section if the slope is less than 95% or greater than 105%.

Precautions

- Do not allow the fill solution to run dry; add fill solution whenever the level falls 25mm below.
- Do not leave the electrode in organic solvents as the tip and body may be damaged. Discard used buffer solutions daily. Do not reuse it.

1

Interference

- The electrode can be stored for up to one week in pH 7.00 or 4.00, not in distilled water.
- For longer storage periods, remove the wetting cap, fill it with 3M KCL solution, and push it onto the tip of the electrode.

2.3 Calibration of Uv-Visible Spectrophotometer

Equipment Details

Instrument/Equipment Calibration Record					
INS/ EQP Name: UV-VISIBLE spectrophotometer					
Department Name: Central Instrumentation Lab					
Make, Soft ware & Version	**Model type & Serial No**	**Beam type (single/double)**	**INS/ EQP.ID No.**	**SOP No.**	**Calibration Frequency**
					Every six months

Tests Performed In UV-Visible Spectroscopy

- Baseline flatness test
- UV region wavelength accuracy test
- Visible region wavelength accuracy test
- %Transmittance of Cuvette
- Control of Absorbance
- Emission lines from the deuterium discharge lamp
- Stray Light measurement
- Resolution power
- Photometric linearity

1**) Baseline Flatness Test**

Measurement configuration parameters:
Reference: No Cuvette
Sample: No Cuvette
Cuvette material : Quartz
Wavelength range: 200-800
Lamp: Deuterium lamp
Detector: PDA detector

WAVELENGTH	MEASURED ABSORBANCE	ACCEPTANCE CRITERIA
200		±0.001
300		±0.001
400		±0.001
500		±0.001
600		±0.001
700		±0.001
800		±0.001

2) Uv Region Wave Length Accuracy Test

Measurement configuration Parameters
Reference: Air (Empty Cuvette)
Sample: Benzene
Recording range: 220-270nm
Lamp : Deuterium Discharge
Detector: PDA Detector

WAVELENGTH	OBSERVED PEAKS AT WAVELENGTH (nm)	ACCEPTANCE CRITERIA
220-270nm		235.9±0.5nm

3) Visible Region Wave Length Accuracy Test

Measurement Parameters:
Reference: Distilled Water
Sample: 0.01% KMno4
Measuring mode: 300 to 600nm
Lamp : Deuterium Discharge
Detector: PDA Detector

WAVELENGTH	OBSERVED PEAKS AT WAVELENGTH (nm)	ACCEPTANCE CRITERIA
300-600nm		310±1nm 525±1nm
		545±1nm

4) %Transmittance of Cuvette

Measurement configuration Parameters

Reference: Empty Cuvette
Sample: Empty Cuvette
Cuvette material : Quartz
Measuring mode: 240nm
Lamp: A deuterium discharge lamp
Detector: PDA Detector

WAVELENGTH (NM)	% TRANSMITTANCE	ACCEPTANCE CRITERIA
240nm		Not less than 80%

5) Control of Absorbance

Absorbance: Visible region

Place dummy Cuvette in sample holder and set %T to "zero." Now remove dummy Cuvette; using fine& coarse control, set a reading of exactly 40.0 on the readout.

Press the Absorbance push button. If the maximum absorbance obtained at λ of 485nm is 0.398 ± 0.002, the photometric calibration of the instrument is confirmed to be proper.

To confirm, repeat the above steps, and set 10.00 on the readout

Press the Absorbance button. If the λ at 485 nm is 1.000±0.002, then the photometric performance in the visible region is correct.

Absorbance: U.V region

- Place blank0.1N H2SO4 Cuvette and 60ppm K2Cr2O7 as sample
- Set λ exactly to 257 nm. If the sample value at the set λ is 0.864±0.005, the instrument measuresabsorbance correctly.

6) Emission Lines From Deuterium Discharge Lamp:

- Measurement configuration Parameters:
- Reference: No Cuvette
- Sample: Empty Cuvette
- Recording range : 400-500, 600-700

THEORETICAL VALUE	OBSERVED VALUE	DIFFERENCE	ACCEPTANCE CRITERIA
486nm			486±0.3nm
656nm			656±0.3nm

7) Stray Light Measurement

- Weigh 1.2g of dried Potassium chloride accurately in a 100 ml volumetric flask and makeup to mark with Double distilled water.
- Measure the absorbance at 200 nm.
- Acceptance criteria: Tolerance limit NLT 2.0

8) Resolution Power

- Prepare 0.02%v/v solution of Toluene and makeup with Hexane.
- Scan the wavelength from 250 to 280nm.

- Maximum absorbance is 269 nm, and Minimum absorbance is 266nm
- Acceptance criteria: Ratio limit NLT 1.5

9) Photometric Linearity

- Weigh 100mg of Potassium chromate in a 100ml volumetric flask and dissolve in 0.05N Potassium hydroxide solution. Makeup with the same solvent.
- From the above solution, take 20ml and makeup to 500ml with 0.05N Potassium hydroxide solution.
- Now prepare dilution of 4,8,16,24,32 µg/ml
- Measure the absorbance at 370nm using blank.
- Acceptance criteria: The plot should be linear, and the regression coefficient (R2) should be NLT 0.999.

2.4 Calibration Of FT-IR

Equipment Details

Instrument/Equipment Calibration Record				
INS/ EQP Name: FTIR				
Department Name: Central Instrumentation Lab				
Make, Soft ware & Version	**Model type & Serial No**	**INS/ EQP ID No.**	**SOP No.**	**Calibration Frequency**
				Every six months

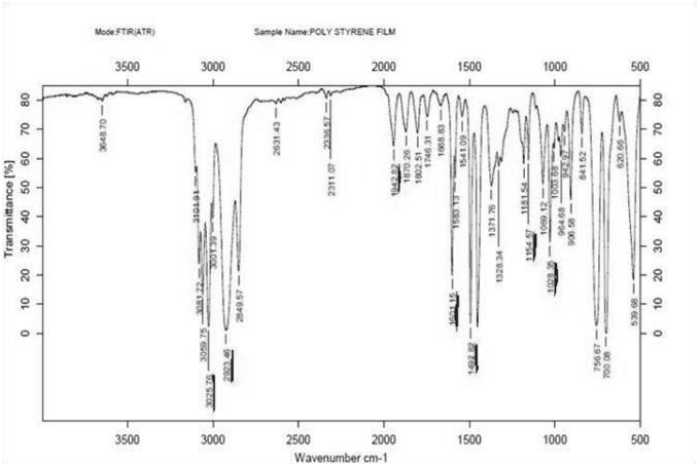
Physical Observation

S.NO	DESCRIPTION	EXPECTED	OBSERVED (pass/fail)
1.	Cabinet finishing	To be free from scratches, stains, dents	
2.	Instrument noise when start up	To be smooth function with out noise	
3.	Top cover fixing	To be without gaps	
4.	Spectrum reading display	To be clear display without blinking	
5.	Lamp check	To be glow through out the measurement	
6.	Anvil and piston set	To be store always in liquid paraffin oil after usage	
7.	Die set	To be clean and free from rust	

Control of Resolution Performance

Identification using reference spectra

The material used: Polystyrene film



Nominal Transmission inima	Observed transmission Minima	Acceptance Criteria
3060.0		±1
2849.5		±1
1942.9		±1
1601.2		±1
1583.8		±1
1154.5		±1
1028.3		±1

2.5 Calibration of Gas Chromatography

Various Calibration Parameters Are:

- Flow rate accuracy
- Column oven temperature accuracy
- System precision
- System precision for headspace autosampler
- Detector linearity
- Detector noise and drift test

1**) Flow Rate Accuracy**

- Connect the digital flow meter to the detector outlet port.
- Set the carrier gas (Helium) flow and wait till it reaches the set flow.
- Note the observed flow in replicate.
- Repeat the procedure for other carrier gases such as Hydrogen and Air.
- Record the result in GC calibration protocol.
- Acceptance criteria: The carrier gas flow rate should be ±10% of the set flow.

S.NO	CARRIER GAS	ACCEPTANCE CRITERIA INML/M
1	Helium	125
2	Hydrogen	40
3	Air	400

2) Column Oven Temperature Accuracy:

- Connect the column to the detector port.
- Place the thermometer probe in the column oven and set the column oven temperature at 40°C.Wait till the temperature stabilizes.
- Note the observed temperature as the probe reads in triplicate throughout 10 m.
- Repeat the procedure for 100°C, 150°C, and 190°C.

Acceptance criteria: The resulting oven temperature from the thermometer display should be within ±2°C of the set temperature

3) System Precision

Preparation of Standard solution:

Transfer 20 ml of Methanol, Ethanol and Acetone into 100ml volumetric flask and makeup with Ethyl acetate

Procedure:

Inject blank, followed by Standard preparation in 6 replicates. Note downthe areas and Retention times.

Acceptance criteria: The %RSD of retention time should be not more than 1.0%& peak area should be not more than 5.0%.

4) System Precision for Headspace Autosampler

Preparation of standard solution:

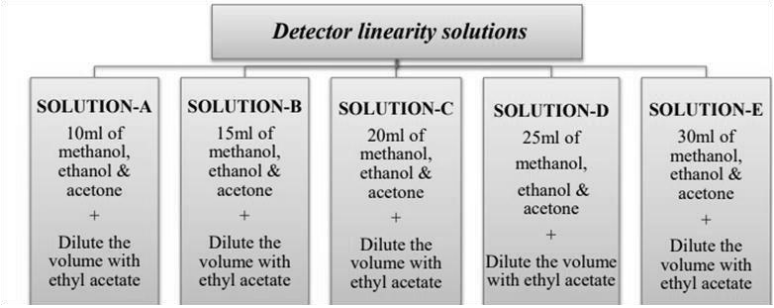
Prepare a standard mixture solution by taking Methylene dichloride (0.6g), Chloroform (0.06g), Trichloroethane (0.08g), and 1,4-Dioxane (0.38g) in a volumetric flask containing about 40ml of Dimethyl formamide. Finally, makeup to volume with DMF(Solution-A)

Procedure:

Take 0.5 ml of standard solution-A in 6 different vials and seal with the septum, then magnetic caps and crimp. Place these vials on the headspace sampler; prepare a blank vial also. Load the vials in a headspace sampler tray. Blank vials followed by the standard vials.

Acceptance criteria: The %RSD of retention time should be NMT 1.0%& peak area should be NMT 15.0%

5) Detector Linearity:



Procedure

Inject blank, followed by Detector linearity solutions and record the peak responses . Finally, draw a standard plot between the concentrations Vs the peak responses.

Acceptance criteria: The plot should be linear, and the regression coefficient (R2) should not be less than 0.99.

Detector Noise and Drift Test

After GC is ready, run the system up to 15 m through the single run. After completion of the run calculate noise and drift through software.

Acceptance criteria: Noise NMT: 100 μV

Drift NMT: 2500 μV/hr

2.6 Calibration of HPLC

Various Calibration parameters are:

- Flow rate accuracy
- Injector accuracy
- System Precision
- Detector linearity
- Injector linearity
- Column oven temperature accuracy

1) Flow Rate Accuracy

- Prime all the solvent lines with Milli Q water.
- Set the flow rate to 0.500 ml/m.
- Wait about 15 m to stabilize the system and ensure the pressure is stable.
- Insert the outlet tubing into a 10 ml volumetric flask and simultaneously start the stopwatch.
- Stop the stopwatch when the lower meniscus reaches the 10 ml mark on the flask.
- Record the elapsed time.
- Similarly, check the flow for 1.0 ml/m and 2.0 ml/m.

Acceptance criteria: The time taken to collect the water should be within ± 2.0% of the actual value

Set Flow	The actual time required to collect up to the mark in m	Acceptance criteria (in m)
0.5 ml/m	20.0	19.6 – 20.4
1.0 ml/m	10.0	9.8 – 10.2
2.0 ml/m	5.0	4.9 – 5.1

2) Injector Accuracy

- Connect the pump and detector inlet with the union.
- Prepare mobile phase consisting of a mixture of water and Methanol (70:30 v/v)
- Set a flow rate of 0.5 ml/m and a run time of 1 m.
- Set the column temperature at 25± 2°C.
- Fill a standard HPLC vial to 2/3rd with Milli-Q water. Seal the vial properly with a cap. Weigh the vial and record the weight as W1 grams.
- Place the vial in the chromatographic system and perform six injections of 50µl volume from this vial.
- Weigh the vial again and note the weight after the injections as W2 grams.
- Calculate the mean volume injected per injection as follows:
- Mean injected volume (µl) = (W1 – W2) ×100/6

Acceptance criteria: The mean injected volume should be 50.0±1.0 µl.

3) System Precision

Standard Preparation:

Accurately weigh and transfer about 60mg of Caffeine into a 100ml volumetric flask. Dissolve and dilute to the volume with the mobile phase.

Transfer 10ml of this solution into a 100ml volumetric flask and dilute to the volume with the mobile phase.

Procedure

Inject blank, followed by standard preparation in 6 replicates. First, note down the areas and retention times. Now calculate the %RSD of retention time and peak areas for six replicates injections.

Acceptance Criteria: The %RSD of retention time & peak area should be <1.0%.

4) Detector Linearity:

Standard Preparation:

Accurately weigh and transfer about 60mg of Caffeine into a 100ml volumetric flask. Dissolve and dilute to the volume with the mobile phase.

Detector linearity solution 1(0.06 mg/ml): Transfer 10ml of Standard Preparation into a 100ml volumetric flask and dilute to the volume with the mobile phase

Detector linearity solution 2(0.048 mg/ml): Transfer 8ml of Standard Preparation into a 100ml volumetric flask and dilute to the volume with the mobile phase.

Detector linearity solution 3(0.03 mg/ml): Transfer 5ml of Standard Preparation into a 100ml volumetric flask and dilute to the volume with the mobile phase.

Detector linearity solution 4(0.24 mg/ml): Transfer 4ml of Standard Preparation into a 100ml volumetric flask and dilute to the volume with the mobile phase.

Detector linearity solution 5(0.012 mg/ml): Transfer 2ml of Standard Preparation into a 100ml volumetric flask and dilute to the volume with the mobile phase.

Procedure

Inject blank, followed by Detector linearity solutions, and record the peak responses of Caffeine standard plot between the concentration Vs. the peak responses.

Acceptance criteria: The plot should be linear, and the regressioncoefficient (R2) should not be less than 0.99.

5) Injector Linearity:

Standard Preparation:

- Accurately weigh and transfer about 60mg of Caffeine into a 100ml volumetric flask.
- Dissolve and dilute to the volume with the mobile phase.
- Transfer 10ml of Standard Preparation into a 100ml volumetric flask and dilute to the volume with the mobile phase.

Procedure:

- Inject 5 µl of the mobile phase as a blank injection.
- Inject 5 µl, 10 µl, 20 µl, 50 µl, and 80 µl of the Standard Preparation and record the peak areas.
- Plot a curve for the volume injected Vs.Peak area.

Acceptance criteria: The plot should be linear, and the regression coefficient (R2) should not be less than 0.99.

6) Column Oven Temperature Accuracy

- It is evaluated with a calibrated digital thermometer at 30°Cand 60°C.
- Place the thermometer probe in the column oven and set the column oven temperature at
- 30°C.
- Wait till the temperature stabilizes.
- Record the temperature displayed on the thermometer.

- Similarly, performs the column oven temperature accuracy test at 60°C.

Acceptance criteria: The resulting oven temperature from the thermometer display should be within ±2°C of the set temperature.

2.7 Calibration of HPTLC

Calibration of HPTLC is done by the following method:

Spotting And Detection Capacity:

Requirements:

i. Alumina glass plates
ii. Sodium salicylate
iii. 96% v/v alcohol

Preparation of Stock Solution:

Stock solution- 1:

Weigh 500mg of sodium salicylate and transfer it into a 250ml volumetric flask, dissolve and dilute with 96% v/v alcohol.

Stock solution- 2:

Weigh 100mg of sodium salicylate and transfer it into a 250ml volumetric flask, dissolve and dilute with 96% v/v alcohol.

Procedure:

Spot 5µl of each solution observe at 254nm and 366nm.

Acceptance:

1) The spots shall be comparable intensity wise
2) Spot due to Stock solution-2 shall be visible at 254nm
3) Spot due to Stock solution-1 shall be visible at 366nm

2B Qualification of Glassware

Introduction

- Qualification is defined as an action of providing that equipment and ancillary systems are properly installed, work correctly, and lead to the expected results. Calibration of an instrument also involves adjusting its precision and accuracy so that its readings come in accordance with the established standard.
- Glassware is commonly calibrated using a liquid of known specific density. The procedure is to determine the mass of liquid the glassware will hold and divide this mass of liquid of the liquid,obtaining the corresponding volume of liquid.

Purpose of Calibration

- Ensure that the readings of equipment or instruments are consistent with other measurements.
- To determine the instruments' measurements' accuracy, precision, reliability, and deviation.
- To establish the reliability of the instrument being used.
- Helps quantify and control errors and uncertainties within various measurement processes to an acceptable level.

Types of Glassware

CLASS A	CLASS B
Economy Grade	Student grade
Calibrated to half the tolerance of class A	Calibrated to double the tolerance of Class B
Havehigh accuracy	Have low accuracy
Recommended quantitative analysis	Recommended for routine use until calibrated

Used directly for analysis purposes and received with calibration certificate	On receiving Class B apparatus allot ID.No and calibrate it

Calibration Procedure for Volumetric Flask and Beaker

1. Weigh accurately a previously dried volumetric flask.
2. Make the volumetric flask up to the mark with purified water.
3. Wipe dry the outside of the volumetric flask and then weigh.
4. Find out the water weight by subtracting the volumetric flask's empty weight from the total weight.

Weight of water(W3) = Total weight of volumetric flask (W2) – Empty volumetric flask weight(W1).

Calculate the volume by taking the correction factor of 0.99602gm. (1 ml of purified water at 250 c = 0.99602 gm).

Record the observation in calibration format.Then, repeat the above calibration three times and take an average sum of three observed values.

Calibration Procedure for Pipette and Burette

1. Weigh accurately previously dried empty beaker.
2. Fill the pipette and burette with purified water up to the mark with the help of a bulb.
3. Wipe dry the outside of the transfer pipette and burette and then transfer the water in a pre-weighed beaker and weigh.
4. Perform the calibration in triplet and calculate and record the average of observed volume

Calculate the difference between label volume and the average observed volume of glassware using the following formula:

The difference in volume = labeled volume – an average of observed volume

- Find out the weight of water by subtracting the empty beaker weight from the total weight.
- Calculate the volume by taking the correction factor of 0.99602gm.
- Weight of dry, empty glassware (W1).....gm
- Weight of glassware and water (W2).....gm
- Weight of water(W3).....gm
- Observed volume of glassware : W2 – W1 ..... gm D where D = 0.99602gm
- Average of 3 observed volume = sum of 3 observations / 3

Tolerance limits on capacity for Volumetric Flasks

S.NO	Capacity(ml)	Tolerance class A(±ml)	Tolerance class B(±ml)
1	5	0.02	0.04
2	10	0.02	0.04
3	25	0.03	0.06
4	50	0.05	0.10
5	100	0.08	0.15
6	200	0.15	0.30
7	250	0.15	0.30
8	500	0.25	0.30
9	1000	0.40	0.50
10	2000		0.80

Tolerance limits on the capacity for Pipettes

S.NO	Capacity(ml)	Tolerance class A(±ml)	Tolerance class B(±ml)
1	1	0.007	0.015
2	2	0.01	0.02
3	3	0.015	0.03
4	4	0.015	0.03
5	5	0.015	0.03
6	10	0.02	0.04
7	15	0.025	0.05
8	20	0.03	0.06
9	25	0.03	0.06
10	50	0.04	0.08
11	100	0.06	0.12
12	200	0.08	0.16

Tolerance limits on capacity for Burettes

S.NO	Normal Capacity (ml)	Scale Sub-division (ml)	Tolerance class A(±ml)	Tolerance class B(±ml)
1	1	0.01	0.006	0.01
2	2	0.02	0.01	0.02
3	5	0.02	0.01	0.02
4	5	0.05	00.02	0.04
5	10	0.02	0.01	0.02
6	10	0.01	0.00	0.05
7	25	0.05	0.03	0.05
8	25	0.1	0.05	0.1
0.9	50	0.1	0.05	0.1
10	100	0.2	0.1	0.2

UNIT-3
VALIDATION OF PHARMACEUTICAL WATER SYSTEM

Water is a component of every pharmaceutical product, so water system must be validated to ensure the consistent production of high quality water. The pharmaceutical industry places a high priority on the quality of water used in production of finished product, intermediate reagent preparation & analytical processes & especially in case of parenteral products where quality of water must be as per Pharmacopoeia. In present scenario the quality of pharmaceutical water is maintained by setting a good pharmaceutical water system and this system encompasses system design qualification, attention of the regulatory requirements which are updated time to time.

Grades of water specified in the USP are classified as:

i. Potable water
ii. Purified water
iii. Water for injection
iv. Sterile water for injection
v. Sterile water for inhalation
vi. Sterile water for irrigation
vii. Sterile bacteriostatic water for injection

Validation Sequence

A. Design Qualification (DQ)

The basic design package should include the following:

i. Flow schematics for the proposed water system showing all of the instrumentation, controls and

valves and component should be numbered for reference.

ii. A complete description of features and functions of the system. This is of critical importance to enable production and quality assurance personnel, who may be unfamiliar with engineering terminology, to fully understand the manner in which the system is to be designed, built, operated, monitored and sterilized.
iii. Detailed specification for the equipment to be used for water treatment and pretreatment.
iv. Detailed specification for all other system components such as storage tanks, heat exchangers, pumps, valves and piping components.
v. Detailed specifications for sanitary system controls and description of their operation.
vi. Specification for construction techniques to be employed where quality is of critical importance.
vii. Procedure for cleaning the system, both after construction and on a routine basis.
viii. Preliminary standard operating procedures (SOP's) for operating, sampling and sterilization. These procedures will be cross referenced to the valve and component numbers on the system schematics.
ix. Preliminary SOP's for filter replacement, integrity testing and maintenance.
x. Preliminary sampling procedures to monitor both water quality and operation of the equipment.
xi. Preliminary system certification procedures.
xii. Preliminary preventive maintenance procedures.

B. Installation Qualification (IQ)-

It ascertains that all the unit components are installed as per the specifications and according to the design drawing. IQ provides construction verification in that established specifications have been complied. This also involves instrument connections, review the instrumentation drawings, review and verify the manual, examination and documentation of wields, inspection for dead legs and pipe slopes, verification of stainless steel passivation and any other information. IQ conforms the "As-Built" drawing and ensures the suitability of the completed system. Absence of leaks shall also be checked. IQ should cover why and how is the water purification system with complete description of system and purification system. Feed water shall be identified in this stage. List out the major components of the system like pump, filters, UV lights, controls, valves, drains, control system etc. and verify adequate to the design specification. Make the list of instruments and controls, calibration of these instruments shall be traceable to the national and international standards. Calibrations of instruments can be performed at the end of IQ process and recorded as a part of IQ or at the beginning of the operational qualification. Once the IQ is complete, system is recommended for operational qualification (OQ).

C. Operational Qualification (OQ)

Considerations of feed water quality, of system capacity, temperature controls, and flow rates are involved in the OQ protocol of the water purification process. It involves an examination of the equipment design to identify features critical to the process and product. The goal of OQ is to evaluate the limits of control within which the validated system is expected to perform.

i. **Components-** Selection should be made with assurance that it does not create a source for contamination intrusion.
ii. **Piping and Installation**- Stainless steel welds should provide reliable joints that are internally smooth and corrosion-free. Piping systems should be installed and sloped in such a way that they are completely self-draining. Complete drainage is important, as it prevents the formation of standing "pools" of liquid that can support the growth of microbes.
iii. **Dead legs**- Dead legs pose two problems for CIP (clean-in-place). First, cleaning fluids must be able to flush out trapped gas pockets in order to wet all the piping surfaces inthe dead legs. Second, fresh cleaning fluid must flush the dead leg to maintain rapidcleaning rates. Dead legs should not be greater in length than six diameters (6D) of the unused portion measured from the axis of the pipe in use.
iv. **Valves**- The most commonly used valves in process piping systems for PW (Purified water) and WFI (Water for injection) used for pharmaceutical manufacturing are diaphragm valves. This is because they are easily CIP-cleanable and provide complete containment of in-process materials. Ball and butterfly valves are also commonly used in water treatment systems.
v. **Pumps**- Pumps should be of sanitary design with seals that prevent contamination of the water. Several types of CIP-cleanable pumps are commonly used in water systems or pharmaceutical manufacturing processes. These include centrifugal, rotary lobe, peristaltic, and diaphragm pumps, of which all but the centrifugal pump provide positive displacement.

vi. **In-line instrumentation**- In-line instruments or sensors are necessary components forautomated processes. For ease of cleaning, sensors should be chosen that directly mount onto vessel nozzles or piping tees with minimum dead leg distances.

vii. **Pressure gauges**- Sanitary diaphragm-style pressure gauges should be used when possible, as they are very cleanable.

viii. **Distillation**- Distillation equipment is used to produce USP WFI-quality water. The distillation process removes dissolved solids not otherwise removed by deionizers or RO units. The condenser must be of a double-tube design to prevent condenser coolant from coming into direct contact with the distillate, thereby causing recontamination.

ix. **Filters**- Water storage tank vent filters must be equipped with a sterilizing air filter in order to prevent the air, which displaces water drawn from the tank, from microbiologically contaminating the water. Filters are commonly used downstream from carbon beds and resin beds and on the incoming water supply line. Membrane filters of 0.2 µm are used to remove bacteria.

x. **Deionizers-**Dionizers use ion exchange resins to remove charged particles. Mixed bed deionizers (containing both cation and anion exchange resins) are commonly used to give the water a final "polishing" treatment.

xi. **Ultraviolet light-** The use of UV light also facilitates the degradation of hydrogen peroxide and ozone. The most effective biocidal wavelength is 253.7 nm. The amount of light at 255 nm emitted by a UV light

decreases with time, so lamps have to be monitored and replaced when necessary.

xii. **Waste water**- Waste liquids shall be introduced to sewers through trapped drains. Drains from equipment shall be designed with an atmospheric break to prevent back siphon age.

D. Performance Qualification (PQ)

The purpose of PQ is to provide rigorous testing of demonstrate the effectiveness and reproducibility of the total integrated process. Three phases approaches shall be used to satisfy the objective of the providing the reliability and robustness of the system in service over an extended period. The three phase validation is regulatoryexpectation.

i. **Phase I:** Test period shall be 2- 4 weeks (14 days minimum) for monitoring the system intensively. During this period the system should operate continuously without failure or performance deviation.

ii. **Phase II**: A further test period of 2-4 weeks (30 days) should be spent carrying out further intensive monitoring, while developing all the refined SOP's after the satisfactory completion of phase I. The sampling scheme should be generally the same as in phase 1. Water can be used for manufacturing purpose during this phase.

iii. **Phase III:** Phase 3 typically runs for one year after the satisfactory completion of phase II. Water can be used for manufacturing purpose during this phase. After completion of phase III of the qualification program of water system, a routine plan should be established based on the results on phase III.

Validation of Pure Steam

The pure steam is produced by the steam generator of the purified water. The steam generator shall be located at a suitable place per approved layout. From this, start the tubing to the different points of use. A system to collect the condensate must be provided for the most important point of use.

The collected condensate could be used to feed the industrial steam generator. The pure steam should be qualified. The WHO guide to GMP requirements clearly says to perform the performance qualification (PQ) of pure steam.

At the time of performance qualification of pure steam generation system, the sample shall be taken from each steam user point and analyzed for three consecutive days. The purified water system must be qualified before starting the qualification of pure steam.

Documents required: Presently, pure steam generators are available where pure water is used as feed water. The validation of the equipment requires the following documents:

- Specifications, test methods and reports for purified water and water for injection.
- Validation reports for purified water system, water for injection system and pure steam generators.

The sampling of Pure Steam: Sampling for Bacterial Endotoxin Test and chemical tests should be done separately. Depyrogenated tubes or bottles should be used for taking the sample for bacterial endotoxin test. Allow the steam to drain for minimum one minute.

Open the cap of the bottle and fill the bottle with steam condensate by holding the bottle in the holder. Gloves should wear into the hands while sampling the pure steam. Tighten the cap of the bottle and mark with the sampling information.

If the sample is not analyzed within 2 hours of sampling, store the sample at 2-8 °C.

Analysis of Pure Steam: Pure steam should be analyzed for following tests:

1. **Non-condensable Gases:** Non-condensable gases are air and carbon dioxide those do not condense with the steam. These are generated due to their presence in the purified water that continuously circulates in the water distribution system. Non-condensable gases should not be more than 3.5%.
2. **Steam Dryness Value**: Dry steam has more energy than the wet steam. Wet steam has water with it and does not have heat energy as dry steam. Dryness of steam is determined by the latent heat. Dryness of the pure steam should not be less than 90%. High moisture content can cause the loss in energy of steam and that may cause the longer sterilization time.
3. **pH:** Steam condensate is analyzed for pH value at 25 ° C. It should be between 5-7.
4. **Conductivity**: Conductivity should be tested with calibrated conductivity meter at 20°C. Conductivity should not be more than 1.3 µS/cm.
5. **Microorganisms**: Steam condensate is tested for microbial contamination using pour plate method. There should not any microbial contamination in the steam condensate.
6. **Endotoxin Test**: Determine the endotoxin in the pure steam condensate and it should not be more than 0.25 EU/ml as in water for injection.

Validation of HVAC System

The HVAC (Heating, ventilation and air-conditioning) system plays an important role in product, personnel,

environment, instrument and machine protection. It also ensures the manufacture of quality pharmaceutical products. HVAC utility is designed to control the level of viable and nonviable particulate exposure that a drug or medicinal device might receive in addition to regulating temperature and relative humidity conditions.

What HVAC Can do?

- Control airborne particles, dust and micro-organisms
- Maintain space moisture (Relative Humidity)
- Maintain room pressure (delta P)
- Maintain space temperature

What is Clean Room?

A room in which the concentration of air borne particle is controlled and which is constructed and used in a manner to minimize the introduction, generation and retention of particles inside the room and in which other relevant parameters.

e.g.. Temperature, humidity and pressure, are controlled as necessary.

Why Clean Room Necessary?

It controls 3 types of contamination transfer

- Air borne contamination
- Direct contamination by personnel, equipment etc.
- Contamination from fluids like cleaning fluids, solutions etc.
- As airborne particulate are reduced, chances of particles entry in the process reduced.
- Protects product, personnel & environment.

How it is Accomplished?

A clean room is continuously flushed with highly filtered air that is forced in through HEPA filters.

Types of Clean Rooms

1*. Horizontal Clean Room*

Horizontal Laminar flow (HEPA filters in a wall force clean air from one side of the room to other.)

2*.Vertical Clean Room*

Vertical Laminar flow (HEPA filters on the ceiling push clean air down to the floor.)

Four Basic Principles of Cleanroom

- Not To Bring Any Dust
- Not To Accumulate Any Dust
- Not To Generate Any Dust
- To Remove Any Dust Quickly

Contamination

It is "the undesired introduction of impurities (chemical, microbiological/foreign matter) into or on to starting material or intermediate – during sampling, production, packaging or repackaging".

Contaminants are:

1. Products or substances other than the product being manufactured.
2. Foreign products.
3. Particulate matter.
4. Micro-organisms.
5. Endotoxins (degraded micro-organisms).

HVAC Consists of

1. Air conditioner
2. AHUs (air handling unit)
3. Dehumidifier / Heater
4. Filters (Pre & HEPA)
5. Dust Extractors
6. Ducting (For delivery of controlled air)
7. Supply Fans
8. Dampers
9. Humidity / Temperature / Pressure sensors
10. Mixer
11. Heating / Cooling Coils

Air Flow Pattern

There are three different types of airflow patterns available for cleanrooms designs

Unidirectional Airflow (Laminar)

The airflow is essentially where the air flows downwards or sideways in an unimpeded path. (NOTE: The laminar flow has not been used recently; instead the term "unidirectional air flow" is used.)

Non-Unidirectional Flow (Turbulent Flow)

where air streams are other than parallel to one another.

Mixed Flow

where airstreams may be parallel in one part of the cleanroom and not in other parts.

Qualification of HVAC

The Validation Master Plan

1. Validation policy
2. Organizational structure of validation activities

3. Facilities, equipment and processes to be validated
4. Documentation format to be used for protocols and reports
5. Planning and scheduling
6. Change control
7. References to documents

User Requirement Specification

1. Size of the equipment
2. Speed of the equipment
3. Effectiveness of the equipment
4. Availability of spares, change parts, and prompt services at reasonable cost
5. Ease of operation, cleaning, and maintenance
6. Materials of construction
7. Auto control system
8. Easy change over

Design Qualification

1. Functional Specification.
2. Technical / Performance specification for equipment.
3. Detailed Air Flow Schematics.
4. Detailed layout drawing of the system

Installation Qualification (IQ)

1. Instrumentation checked against current engineering drawings and specifications.
2. Properly served by the required utilities.
3. Verification of materials of construction.
4. Installation of equipment and with piping.
5. Calibration of measuring instruments.
6. Components are installed at specified location.

Operation Qualification

1. Ability to provide air of sufficient quality and quantity to ensure achievement of specified clean room conditions.
2. Ability to maintain temperature, relative humidity and pressure set points.
3. Ability to maintain any critical parameters stated in the DQ consistently.
4. Includes the tests that have been developed from knowledge of processes, systems and equipment.

Performance Qualification

1. Test to include a condition or set of conditions encompassing upper and loweroperating limits.
2. PQ is used to demonstrate consistent achievement of critical parameters over time. (under manufacturing conditions)
3. Any changes to the HVAC system should be revalidated before proceeding to the PQ phase.

Validation

Validation is establishing documented evidence which provides a high degree of assurance that a specific process, equipment, material, activity or system consistently produces a product meeting its predetermined specifications and quality attributes.

Validation Parameters

1. Air flow measurement
2. Room air changes per hour.
3. Filter Integrity Testing (HEPA Leak test)
4. Pressure Differentials
5. Particulate count measurement

6. Recovery test
7. Temperature and Relative Humidity
8. Air Flow Pattern
9. Microbial Count

Air Flow Pattern

1. Take the titanium tetra chloride stick.
2. Burn the stick.
3. Place the burning stick in front of running Air Handling Unit (AHU).
4. Observed the flow of air with the help of smock distribution in the room.
5. Make chart diagram of the flow of air in the room for each room.
6. The distribution of smoke is observed. It should be uniform.

Air flow Velocity & Changes per Hour

For this test, the area of HVAC is divided into four hypothetical grids and the air velocity is measured at each grid and then the average air velocity (V) is calculated.

Record the velocity readings taken at the centre of the grids, and at the junction of dividing lines (centre of HEPA Filter) .Calculate the Average Velocity as

$V = (V1+V2+V3+V4) / 4$

V = Velocity observed at each point

Now calculate the area of the filter by multiplying the length and width of the filter in feet.

$A = l \times w$

l = length of HEPA filter

w = width of HEPA filter

Class	Number of air changes /per hour
Class 100	NLT 250
Class 1000	60 ± 10 %
Class 10000	40.± 10 %

Calculate the total air volume per minute supplied in the clean room by the following formula:

T = A x V

A = Area of HEPA filter in square feet

V = Average air velocity in feet per minute

Calculate the total air in the room multiplying the length, width and height of the room in feet.

Volume = L x W x H

Now we can calculate the Air Changes per hour using the following formula:

Air Changes per Hour = T X 60/ Volume

Filter Leak Test

1. Place the velometer at the front of AHU unit.
2. Check the velocity of air to the all corner of the AHU.
3. The air velocity should be within the higher limit of HEPA filter.
4. In case it is found to exceed the upper limit, a gas cut (silicon) is used to decrease the leakage. Thermal Anemometers Velometer Rotating Vanes

Particles Count

- Useful in detecting significant deviations in air cleanliness from qualified processing classifications.
- Immediate understanding of air quality can be realized
- Useful as a tool for qualification and monitoring before /during and after operations.

On the air system before one hour of test operation.

1. Take the suitable particle counter and operate it to check the particles in the room at non-working operation.
2. Collect the information from particle counter and fill them in the format.
3. Operate the particle counter when work is on progress in the area. The particles should be count when more than one-hour work has been progressed in the area. Record the data in the format.
4. Operate the particle counter for all the room maintaining grade A, grade B, grade C & grade D.

Pressure Drop across the HEPA and Fine filters of Air Handling Unit

Objective:

The purpose of this test is to check the Clogged or clean condition of the across HEPA
filters, Fine Filter and Pre - filter, of the Air Handling Unit.

Test Equipment:

Differential pressure Transmitter or Manometer

Procedure for HEPA, Fine and Pre Filters

1. Ensure that the differential pressure transmitter is connected to before the filter and after the filter.
2. Check the status of the filter whether the filter is in clean condition or Clogged condition.

Acceptance Criteria:

HEPA, Pre and Fine filters should be in clean condition.

Temperature and Relative Humidity Test

Objective:

To demonstrate the ability of the HVAC system to provide temperature and Relative Humidity within the specified range.

Test Equipment:

Temperature and Relative Humidity Sensor Display Unit for Temperature and Relative Humidity

Procedure:

Observe the temperature and relative humidity through respective display unit wherever installed. Use Hygrometer to check the reading of Temperature and RH in other rooms.

Temperature and RH in the area to be checked and recorded in Static as well asDynamic Condition.

Static Condition:

In static condition all the machines shall be kept switched 'OFF'. Only restricted manmovement shall take place.

Dynamic Condition:

In dynamic condition machines having maximum loads shall run and restricted man movement shall take place.

Acceptance Criteria:

Temperature and relative humidity should meet the requirement as specified in system specification.

Sound level Test

Objective

To verify that the sound level is in limit in the clean room area.

Test Equipment

Sound Level Meter, duly calibrated with traceability to national / international standard.

Procedure:

Take the reading at 5 locations in the room and take the average of the sound in the unit of decibels.

Acceptance Criteria:

The clean room or clean zone shall meet the acceptance criteria for sound level as mentioned below

Cleanliness class	Sound level class (db)
Class 100 /ISO 5	NMT 60
Class 1000 /ISO 7	NMT 80
Class 10000 /ISO 8	NMT 80

Air Borne Viable Particle Monitoring

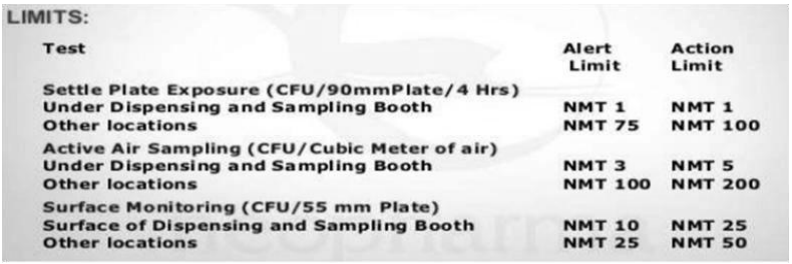
Objective

To determine the air borne microbial contamination level in critical area.

Air borne microbial count by settling plate exposure method:

Pre incubated SCDA Media plates shall be exposed in Locations mentioned for 4 hours and incubated for 48 hours at 30°C to 35°C followed by next 72 hours at 20°C to 25°C.Record the results in respective format. PDA plates shall be exposed weekly to monitor the fungal counts. SCDA plates shall be incubated once in fifteen days to monitor the anaerobic Microorganisms

Acceptance Limit



LIMITS:

Test	Alert Limit	Action Limit
Settle Plate Exposure (CFU/90mmPlate/4 Hrs)		
Under Dispensing and Sampling Booth	NMT 1	NMT 1
Other locations	NMT 75	NMT 100
Active Air Sampling (CFU/Cubic Meter of air)		
Under Dispensing and Sampling Booth	NMT 3	NMT 5
Other locations	NMT 100	NMT 200
Surface Monitoring (CFU/55 mm Plate)		
Surface of Dispensing and Sampling Booth	NMT 10	NMT 25
Other locations	NMT 25	NMT 50

Validation of Compressed Air

- Definition of compressed air:
- Commonly called Industry's Fourth Utility
- Air that is condensed and contained at a pressure that is greater than the atmosphere
- The process takes a given mass of air, which occupies a given volume of space, and reduces it into a smaller space. In that space, greater air mass produces greater pressure. The pressure comes from this air trying to return to its original volume
- It is used in many different manufacturing operations. A typical compressed air system operating at 100 psig (7 bar) will compress the air down to 1/8 of its original volume.
- Compressed air is an important component of pharmaceutical manufacturing facilities
- It provides many of the air types necessary for a manufacturing facility to function, including: breathing air , motive air for machines , process air , analytical air and Product Direct Impact , or "cGMP" air
- The application for which the compressed air will be used will dictate the level of air quality that is appropriate for use

Types of Compressed Air System

I. Conventional oil lubricated compressors- For operating instruments and machinery where no contact with product being manufactured is involved.
II. Oil free compressed air system- Used in clean room areas.

Validation Protocol

A. Installation Qualification (IQ)

This section establishes documented verification that key aspects of equipment adhere to approve design intentions and recommendation of manufacturer have been suitably consider. In addition to the common requirements outlined in the "General" section, the following are required for Distribution systems

The piping should be supported, labeled, and sloped to drain completely

1. Oil Free Compressor

- Check specification on purchase order and actual delivery specification
- Verify that no oil or other lubricant is used in the compressor
- Check that all required utility requirements have been met and connected properly
- Check whether pre-start up procedures were performed
- Check whether all critical instruments have been calibrated
- Document above all

2. Compressed Air Storage Tank

- Confirm that the material of construction is as per specification
- Check the capacity of the tank against purchase specification
- Carry out a pressure hold test to determine whether the leak rate is within specification
- Examine the cleaning procedure adopted for the tank and observation made at the time of cleaning
- Check all pressure rates for tank against the purchase specification
- Calibrate all critical instrumentation on storage tank

3. Distribution System

- Confirm the material of construction and design parameter specified by the company
- Compare the drawing of the system with "as-built" drawing to show whether any modification have been made and note the modifications.
- Pressure test the system to confirm its integrity and record the result
- Examine the cleaning procedures after installation

B. Operational Qualification (OQ)

- This section establishes that there is a documented verification that the installed system functions as a specified and that there is a sufficient documentary evidence to demonstrate
- The OQ protocol will outline tests to study capacity and pressure during estimated minimum and maximum use
- All use points supply the specified pressure prior to any pressure reducing valves or equipment

- All use point supply the volume of gas as specified
- Each peak load use point as specified by use or equipment

Identification Test

- Procedure: Use gas chromatograph for the identification of compressed air. For comparison, an air standard should be used.
- Acceptance criteria: The identity test for oil-free compressed air must show a chromatogram with no additional peaks other than those obtained with the air standard.
- Frequency: Initial val. – once at all critical points
- Revalidation- once at all critical points
- System supply reliability test Document the system pressure twice a day over a period of about 30 working days. The data generated should be compared with the specifications of the system.

C. Performance Qualification (PQ)

This section gives documented verification that the equipment performance in its normal operating environment is consistently exactly as specified in User Requirement Specification (URS)

Each point of use will be tested at least three times over 10 working days. Every use point of the system must be tested several times over the course of the study.

PQ includes the following Tests

- NON VIABLE PARTICLE COUNT
- VIABLE PARTICLE COUNT
- MOISTURE CONTENT
- OIL CONTENT

- HYDROCARBON MONITORING
- PURITY ANALYSIS FOR NITROGEN
- PURITY ANALYSIS FOR OXYGEN

Moisture Content

- **Procedure**: use dew point meter to determine moisture content from critical supply unit
- **Acceptance criteria**: The dew point of compressed air less than or equal to -10°C, or less than the lowest temperature to which the system is exposed
- **Frequency** Initial val. – 1test/day for first 30days at all critical supply points each day. Revalidation- 1test/month at each critical supply point.

Dew Point Measurements Test

What is Dew point?

- The dew point is the temperature below which the water vapor in air at constant barometric pressure condenses into liquid water at the same rate at which it evaporates.
- The condensed water is called dew when it forms on a solid surface.

Pressure Dew Point

- The term "pressure dew point" refers to the dew point temperature of a gas at pressures higher than atmospheric pressure. When addressing dew point in pressurized compressed air, the correct terminology is actually "pressure dewpoint," but this is often shortened to "dew point" in common usage.
- Dew point is performed using a calibrated Dew Point Transmitter connected to the compressed air system – giving instantaneous results.

Why is dew point so important in pharmaceutical applications?

- Compressed air may be used for a number of applications in the pharmaceutical industry, such as raw material transport, processing equipment, pneumatic power sources, and cleaning.
- The importance of knowing the dew point in a compressed air line may be critical for some applications but less relevant for others. For example, bulk solid and powder conveyers used for moving product rely on sufficiently dried and filtered air in order to perform their function properly and prevent product contamination.
- Continuous monitoring and control of dew point is often a requirement for instrument air, drying processes, packaging, and actuating process control valves.
- The risks associated with letting dew point levels go unchecked can include equipment failure, condensation in process lines and on finished product, and the potential for bacterial formation.
- ***Why is dew point so important in laboratory environments?***
- Laboratory environments are often designed to maintain a controlled atmosphere in order to eliminate airborne contaminants and any sources of error that may interfere with testing.
- Dewpoint can be an important parameter to control.
- This is usually accomplished through the environmental control system and has little to do with compressed air. Some lab equipment, such as glove boxes, may require their feed gas to meet an

established dewpoint level in order to maintain the inert atmosphere of the chamber

Oil Content

- **Procedure**: Using the oil indicators
- **Acceptance criteria**: Oil content of oil free compressed air should be NMT 0.01ppm
- **Frequency**: Initial val. – 1test/day for first 30days at all critical supply points each day. Revalidation- 1test/month at each critical supply point.

Non-viable Particle Count

- **Procedure**: The outlet of the supply point is opened for 5min. Adjust to a volume flow of about 30l/min. The particulate counter is connected to the outlet, at the maintained flow a min. volume of 90lits. Is monitored. Each supply point should be investigated in the same way.
- **Acceptance criteria**: Nonviable particulate counts must be ≤ 100/ft3 of 0.5µ or larger at all critical use points
- **Frequency**: Initial val. – once for each supply point ,Revalidation- every 3 months

Viable Monitoring

Acceptance criteria: (not needed of integrity tested final filter is in place) less than 0.03 CFU/ft3 or less than 1 CFU/m3

Hydrocarbon Monitoring

Acceptance criteria: should show less than 0.2 mg/m3 (25 mg/125 liters) detected. (the lower limit of a Dragger tube)

Identity and Purity (Nitrogen)

Acceptance criteria: Not less than 99.0% nitrogen by volume. Not more than 0.001% Carbon Monoxide. No appreciable odor

Identity and Purity (Oxygen)

Acceptance criteria: Not less than 99.0% Oxygen by volume. No appreciable odor

Final report: Depending on IQ, OQ and PQ data final report is made and that will indicate whether your system is validated or not.

Validation of Nitrogen Gas

Nitrogen Gas is a critical component in the production of pharmaceutical industry and effects on the quality of the end product. Therefore, it should be monitored to ensure that desired quality of the compressed air is using in production. The most common gases used in Pharmaceutical Industries are compressed air used for instruments or product contact, and Nitrogen used for providing an inert gas in the vial, ampoule or WFI tanks and used for creating an inert pressure pad in processes where solvents are present

The Quality of Nitrogen Gas is important to ensure that product is safe.

The most important parameters in specifying Nitrogen Gas quality are:

- Purity
- Gases such as O2, CO & CO2
- Odor
- Dew Point
- Oil Content
- Particulate matter
- Moisture Content

- Viable Count
- Identification Test

Test to Be Performed

1. Dew point
2. Oil content
3. Particulate matter
4. Moisture

Dew Point

The dew point temperature or saturation temperature can be defined as the temperature at which water vapour begins to condense .The quantity of any gas in a mixture can be expressed as a pressure .Gas of unknown water vapour concentration is passed over a temperature –controlled surface. The surface is cooled until condensation forms .The temperature at which condensation forms is called the Dew Point temperature .Because there is a unique correlation between temperature and saturation vapour pressure, measuring the dew point temperature of a gas is a direct measurement of the partial pressure of water vapour. Desiccant drying system absorbs water vapour from the air stream and can produce air with a dew point of -40^{o}c and drier if required

Oil Content

- A Nitrogen Oil content test is a measure of the Oil Content of Nitrogen systems.
- The test can accurately determine the amount of Oil flowing in a Compressed Air stream and assess whether the system complies with relevant requirements.

- Many Compressed air systems are supplied using lubricated compressors. These Compressors often blow small particles of Oil throughout the system, which can cause a range of problems for components when the Oil emulsifies with water in the system.
- Oil free air is generally required for a Nitrogen System and an Oil content of less than 0.01 mg/m3 is generally specified.

Particulate Matter

- In many of these applications, Nitrogen is in direct contact or indirect contact with product and the impurities in the Nitrogen may contaminate the product which can result in change of colour and taste, reduced shelf life, in addition to exposure to bacteria and other microorganisms can result in product recalls.
- Compressed air, which is generated on site by pulling in ambient air and compressing it, contains water vapor, particulate matter (atmospheric air typically contains 140-150 million dirt particles/m3).
- More importantly, the filtration systems that are employed are designed to protect process equipment from large slugs of water, oil, rust and pipe scale with a nominal rating of 25 to 40 micron and are not capable of removing submicron contaminates. Nitrogen has the particulate matter of < 5 mg/m3.

Moisture

- All atmospheric air contains some water vapor which will begin to condense into liquid water in the Nitrogen gas system when the air or gas cools past the saturation point, i.e., the point where it can hold no

more water vapor. The condensed moisture must be removed by a separator and trap.

- Moisture in Nitrogen used in a manufacturing plant causes problems in the operation of pneumatic air systems, solenoid valves and air motors.
- This moisture causes rust and increased wear of moving parts as it washes away lubrication. Corrosion of gas operated instruments from moisture can give false readings, interrupting or shutting down plant processes. The malfunctioning of these controls due to rust, scale, and clogged orifices can result in damage to product or in costly shutdowns. Additionally, the freezing of moisture in control lines in cold weather commonly causes faulty operation of controls. Moisture content should be less than < 67ppm v/v for Nitrogen Gas System.

Cleaning Validation

Cleaning validation is documented evidence with a high degree of assurance that one can consistently clean a system or a piece of equipment to predetermined and acceptable limits. The objectives of good manufacturing practices (GMP) include the prevention of possible contamination and cross-contamination of pharmaceutical starting materials and products. Pharmaceutical products can be contaminated by a variety of substances such as contaminants associated with microbes, previous products (both active pharmaceutical ingredients (API) and excipient residues), residues of cleaning agents, airborne materials, such as dust and particulate matter, lubricants. Adequate cleaning procedures play an important role in preventing contamination and cross-contamination. Validation of cleaning methods provides

documented evidence that an approved cleaning procedure will provide clean equipment, suitable for its intended use.

Advantage of Cleaning Validation

- Assurance of quality & safety.
- Government regulations.
- Product integrity
- Microbial integrity
- Cross contamination integrity
- Batch integrity
- Equipment reuse
- Reduction of quality costs
- Making good business sense.
- Less down time, fewer batch failures and may operate / clean more efficiently.

Cleaning Mechanism

Several basic mechanisms exist to remove residues from equipment, including:

- Mechanical action refers to physical actions such as
- Brushing
- Scrubbing
- pressurized water to remove particulates.
- Dissolution involves dissolving residues with a suitable solvent.

The most common and practical solvent is water because of its advantages:

- Water is non-toxic, cheap, does not leave residues, and is environment friendly. However, in some cases it may be preferable to use a non-aqueous solvent or a combination of both aqueous and non-aqueous solvents due to the solubility characteristics of the

materials. Alkaline or acidic solvents, for example, can enhance dissolution of the materials and could be advantageous.

- Detergency requires the use of surfactant, usually in an aqueous system. Detergents act in four different ways:
- Wetting agents
- Solubilizes
- Emulsifiers,
- Dispersants.
- Usually detergents possess all these properties which broaden their action.
- Chemical reactions such as oxidation and hydrolysis in which the residues are chemically changed. Example: Sodium Hypochloride

Cleaning Agent

Detergents should facilitate the cleaning process and be easily removable. Detergents that have persistent residues such as cationic detergents which adhere very strongly to glass and are difficult to remove, should be avoided where possible.

- The composition of the detergent should be known to the manufacturer and its removal during rinsing, demonstrated.
- Acceptable limits for detergent residues after cleaning should be defined. The possibility of detergent breakdown should also be considered when validating cleaning procedures.
- Detergents should be released by quality control and, where possible, should meet local food standards or regulations.

Example of few solvents listed below-

- Aqueous cleaning- water
- organic solvent- acetone, methanol, ethyl acetate
- water surfactant- SLS, SDS
- chelants solvent (acid" EDTA, NTA, SHMP/baseNaOH, KOH)
- Acid- Glycolic acid, citric acid
- oxidant- NaOCl, H2O2

Cleaning Validation Program

A. Selection of cleaning Level (Type)
B. Selection of cleaning method
C. Selection of sampling method
D. Selection of Scientific basis for the contamination limit (acceptance criteria)
E. Selection of Worst case related to the equipment
F. Selection of Worst case related to the product
G. Establishing the storage period after cleaning (hold time study)
H. Selection of analytical method
I. Documentation

A. Selection of cleaning level (type)-

i. **Type A (Minor)-** This type of cleaning take place between two batches of same product or between different strengths of the same product. For minor cleaning, cleaning validation is not required, since cross contamination is not an issue.
ii. **Type B (Major)-** This type of cleaning take place between two products. In this case, validation of the effectiveness of the cleaning procedure in removing residues to the required level is mandatory.

B. Selection of cleaning method

i. Manual cleaning
ii. Semi-automatic procedures
iii. Automatic procedures
iv. CIP (Clean-in-place)
v. COP (Clean-out-of-place)

Manual Cleaning Method

- Difficult to validate
- Most extensive and elaborate cleaning procedures are required.
- A high quality and extensive training program is required.
- The risk involved in manual cleaning processes is taken care of with following:
- Proper washroom design with drying, protection and storage requirement.
- Detailed cleaning SOP
- Training / Qualification of cleaning operators
- ***Clean-In-Place (CIP) Method***
- Cleaning of the equipment is performed in place without disassembling
- Cleaning process may be controlled manually or by an automated program.
- Very consistent and reproducible cleaning method.
- Can be validated readily.
- Being a closed system visual inspection of all components is difficult.

Clean-Out-Of-Place (COP) Method

- Cleaning of disassembled equipment is performed in a central washing machine.

- The washing machine also requires validation such as the temperature, ultrasonic activity, cycle time, cleaning operation sequence, detergent quantity dispensed etc.

C. Selection of Sampling Method

Generally, there are two types of sampling that are accepted. The most desirable is the direct method of sampling the surface of the equipment, another method being the use of rinse sampling. **i. Rinse samples (indirect method)-**

This method is based on the analytical determination of a sample of the last rinsing solvent (generally water) used in the cleaning procedure. The volume of solvent used for the last rinse must be known to allow for the quantitative determination of the contamination.

Advantages

- Ease of sampling.
- Evaluation of entire product contact surface.
- Accessibility of all equipment parts to the rinsing solvent.
- Best fitted to sealed or large scale equipment and equipment which is not easily or routinely disassembled.

Disadvantages

- No physical removal of the contaminant.
- The rinsing solvent may not reach inaccessible or occluded part of equipment.
- Use of organic solvents for water insoluble materials.

ii. Swab Sampling

It is also know as direct surface sampling method. This method is based on the physical removal of residue left over on a piece of equipment after it has been cleaned and dried. A swab wetted with a solvent is rubbed over a previously determined sample surface area to remove any potential residue, and thereafter extracted into a known volume of solvent in which the contaminant active ingredient residue is soluble. The amount of contaminant per swab is then determined by an analytical method of adequate sensitivity.

Advantages

- Direct evaluation of surface contamination.
- Insoluble or poorly soluble substances may be physically removed from the equipment surfaces.
- Hard-to-clean but accessible areas are easily incorporated into the final evaluation.

Disadvantages

- Difficult to implement in large-scale manufacturing equipment.
- Extrapolation of results obtained for a small sample surface area to the whole product contact surface area.

D. Selection of scientific basis for the contamination limit (acceptance criteria):

i. Approach 1 (Dose criterion)- No more than 0.1% of the normal therapeutic dose of one product will appear in the maximum daily dose of a subsequent product. NOEL (No observed effect level) is amount of drug in mg that does not have any effect on human health.
ii. Approach 2 (10 ppm criterion)-No more than 10 ppm of one product will appear in another product iii.

Approach 3 (Visually clean criterion)- No residue should be visible on equipment after cleaning. Spiking studies should determine the concentration at which most active ingredients are visible. This criterion may not be suitable for high potency, low-dosage drugs. The acceptance limit calculation for chemical residue shall be based on Dose Criteria and 10 ppm Criteria.

E. Selection of worst case related to the equipment:

Bracketing by equipment should be done only when it is similar equipment, or the same equipment in different sizes (e.g. 300-L, 500-L and 1000-L tanks). An alternative approach may be to validate the smallest and the largest sizes separately. The worst case for a group of equipment is represented by the equipment with the larger product contact surface and the hardest-to-clean locations.

F. Selection of worst case related to the product:

Only one product out of a group of product processed in a piece of equipment is selected for the cleaning validation study, based on the lowest solubility of the active ingredient and its therapeutic dose.

G. Establishing the storage period after cleaning (hold time study):

The objective for establishing time limit between equipment cleaning and reuse is to ensure that the equipment remains clean till the next use. This needs demonstration that there is no microbial proliferation in cleaned equipment's during storage. For establishing the time limit, the equipment should be dried. Initial swab samples for surface should be taken. Thereafter, the equipment should be protected as prescribed in the SOP and stored in its designated area.

Periodic samples of product contact surface for microbiological contamination should be taken. (1st day, 2nd day, 3rd day etc.) Based on the data generated establish the acceptable time limit.

H. Selection of analytical method:

The Basic Requirements for the Analytical Method.

a. The sensitivity of the method shall be appropriate to the calculated contamination limit.
b. The method shall be practical and rapid, and, as much as possible use instrumentation existing in the company.
c. The method shall be validated in accordance with ICH, USP and EP requirements.
d. The analytical development shall include a recovery study to challenge the sampling and testing methods.

i. Specific Methods

- Chromatographic methods such as GC, HPLC etc.
- Thin layer chromatography
- Specific ion meter of the above methods, chromatography methods are the methods of choice, as they separate analytes, are highly specific, highly sensitive, and quantitative. But the methods are costly and time consuming.

ii. Non-specific Methods

- Spectrophotometric methods in the visible, infrared, or UV ranges
- Total organic carbon (TOC)
- Other Methods For monitoring cleaning procedure TOC method is used. It offers at a moderate cost and in

addition to its rapidity, a detection capability down to the ppb range.

I. Documentation

- Detailed cleaning procedure(s) are to be documented in SOPs.
- A Cleaning Validation Protocol is required to define how the cleaning process will be validated.
- Depending upon the complexity of the system and cleaning processes, the amount of documentation necessary for executing various cleaning steps or procedures may vary.
- When more complex cleaning procedures are required, it is important to document the critical cleaning steps. In this regard, specific documentation on the equipment itself which includes information about who cleaned it, when the cleaning was carried out, the product which was previously processed on the equipment being cleaned should be available. However, for relatively simple cleaning operations, the mere documentation that the overall cleaning process was performed might be sufficient.
- Other factors such as history of cleaning, residue levels found after cleaning, and variability of test results may also dictate the amount of documentation required. For example, when variable residue levels are detected following cleaning, particularly for a process that is believed to be acceptable, one must establish the effectiveness of the process and of the operator performance. Appropriate evaluations must be made, and when operator performance is deemed a problem, more extensive documentation (guidance) and training may be required.

- A Final Validation Report should be prepared. The conclusions of this report should state if the cleaning process has been validated successfully.

Cleaning in Place (CIP):

Clean-in-place (CIP) is a method of cleaning the interior surfaces of pipes, vessels, process equipment, filters and associated fittings, without disassembly.

The U.S. Food and Drug Administration published a CIP regulation in 1978 applicable to pharmaceutical manufacturing.

The benefit to industries that use CIP is that the cleaning is faster, less labor-intensive and more repeatable, and poses less of a chemical exposure risk. CIP started as a manual practice involving a balance tank, centrifugal pump, and connection to the system being cleaned. Since the 1950s, CIP has evolved to include fully automated systems with programmable logic controllers, multiple balance tanks, sensors, valves, heat exchangers, data acquisition and specially designed spray nozzle systems. Simple, manually operated CIP systems can still be found in use today.

Depending on soil load and process geometry, the CIP design principle is one of the following:

- Deliver highly turbulent, high flow-rate solution to effect good cleaning (applies to pipe circuits and some filled equipment).
- Deliver solution as a low-energy spray to fully wet the surface (applies to lightly soiled vessels where a static sprayball may be used).
- Deliver a high energy impinging spray (applies to highly soiled or large diameter vessels where a dynamic spray device may be used). Elevated

temperature and chemical detergents are often employed to enhance cleaning effectiveness.

Factors affecting the effectiveness of the cleaning agents-

i. Temperature of the cleaning solution- Elevating the temperature of a cleaning solution increases its dirt removal efficiency. Molecules with high kinetic energy dislodge dirt faster than slow moving molecules of a cold solution.
ii. Concentration of the cleaning agent- A concentrated cleaning solution will clean a dirty surface much better than a dilute one due to the increased surface binding capacity.
iii. Contact time of the cleaning solution- The longer the detergent contact period, the higher the cleaning efficiency. After some time, the detergent eventually dissolves the hard stains/soil from the dirty surface.
iv. Pressure exerted by the cleaning solution (or turbulence)- The turbulence creates an abrasive force that dislodges stubborn soil from the dirty surface.

CIP cycle- A typical CIP cycle consists of many steps which often include (in order):

Pre-rinse with WFI (water for injection) or PW (purified water) which is performed to wet the interior surface of the tank and remove residue. It also provides a non-chemical pressure test of the CIP flow path. ii. Caustic solution single pass flush through the vessel to drain. Caustic is the main cleaning solution. iii. Caustic solution re-circulation through the vessel. iv. Intermediate WFI or PW rinse v. Acid solution wash – used to remove mineral precipitates and protein residues. vi. Final rinse with WFI or PW – rinses to flush out residual cleaning agents. vii. Final air blow – used to remove moisture remaining after CIP cycle.

Bioreactors, fermentors, and mix vessels- CIP is commonly used for cleaning bioreactors, fermenters, mix vessels, and other equipment used in biotech manufacturing, pharmaceutical manufacturing and food and beverage manufacturing. CIP is performed to remove or obliterate previous cell culture batch components. It is used to remove in-process residues, control bioburden, and reduce endotoxin levels within processing equipment and systems.

UNIT - 4
ANALYTICAL METHOD VALIDATION AS PER ICH AND USP

Introduction

- Validation is the documented act of proving that any procedure,process, equipment, material, activity or system actually leads to the expected result.
- Analytical method validation is documenting/proving that an analytical method provides analytical data acceptable for the intended use.
- A pharmaceutical drug product must meet all its specificationsthroughout its shelf-life.
- The method of analysis used must be validated. This is required toensure the product's safety and efficacy through out all phases of its shelf-life.

Objective

- The main objective of analytical validation is to ensure that a selected analytical procedure will give reproducible and reliable results that are adequate for the intended purpose.
- This applies to all the procedure either pharmacopoeial or non-pharmacopoeial.

Types of analytical procedures to be validated

The required validation parameters also termed " analyticalperformance characteristics", depends upon the type of analytical method.

Pharmaceutical analytical methods are characterized into 5 general types

- Identification tests
- Potency assays
- Limit tests for the control of impurities
- Impurity tests- quantitative
- Specific tests

Validation Parameters as per ICH/USP

USP

- Specificity
- Linearity or range
- Accuracy
- Precision
- Limit of detection
- Limit of quantitation
- Ruggedness
- Robustness

ICH

- Specificity
- Linearity
- Range
- Accuracy
- Precision
- Limit of detection
- Limit quantitation
- Robustness

1. Accuracy

Definition: "The accuracy of an analytical procedure is the closeness of agreement between the values that are accepted

either as conventional true values or an accepted reference value and the value found."

Determination

Assay

i. Drug substance
ii. Drug product

Impurities (Quantitation)

Recommended data: Assessed by 9 determinations over a minimum of 3 concentration levels covering a specified range.

Limit

i. Typical accuracy of the recovery of the drug substance is expected to be about 99 – 101%.
ii. Typical accuracy of the recovery of the drug product is expected to be about 98 – 102%.

2. Precision

Definition: "The closeness of agreement (degree of scattering) between a series of measurements obtained from multiple samplings of the same homogeneous sample."

Precision Includes

- Repeatability
- Intermediate Precision
- Reproducibility

Repeatability

- Repeatability expresses the precision under the same operating conditions over a short time interval.
- Repeatability should be assessed using a minimum of 9 determinations covering the specified range.

Intermediate Precision

Intermediate precision expresses variations within laboratories, such as different days, analysts, equipment, etc.

Reproducibility

Reproducibility expresses the precision between laboratories.

The following parameters should be reported

a. Standard deviation.
b. Relative standard deviation.

3. Limit of Detection

The lowest amount of analyte in a sample can be detected but not necessarily quantitated.

4. Limit of Quantitation

The lowest amount of analyte in a sample can be quantitatively determined with suitable precision and accuracy.

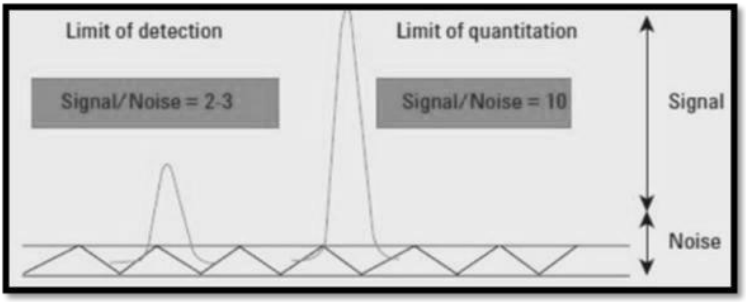
Determination of LOD and LOQ

1. Limit of detection

- Method
- Based on visual examination.
- Based on a standard deviation of response and slope.
- Signal-to-noise ratio 2:1 or 3:1

2. Limit of Quantitation

- Method
- Based on visual examination.
- Based on the standard deviation of response and slope.
- Signal-to-noise ratio 10:1



5. Specificity

Definition: Specificity is the ability to assess the analyte unequivocally in presence of components which may be expected to be present.

Determination

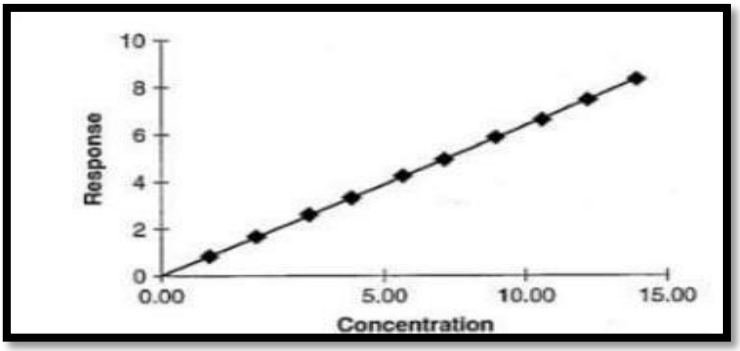
- Identification tests
- Assay and impurity test(s)
- Impurities are available
- Impurities are not available

6. Linearity

Definition: The ability of the method to obtain test results that are directly proportional to concentration within a given range.

Method: dilution of stock solution/separate weightings

- Minimum of five concentrations are used.



7. Range

Definition: The interval between the upper and lower concentrations of analyte in the sample that have been demonstrate to have a suitable level of precision, accuracy, and linearity.

- Established by confirming that the method provides an acceptable degree of linearity, accuracy, and precision.
- Specific range dependent upon intended application of the procedure.

Assay: 80 to 120% of test concentration.

- Content uniformity: 70 to 130% of test concentration.
- Dissolution: 20% to 120%
- Impurities reporting level: 120% of specification limit (with respect to test concentration of API)

8. Ruggedness

Definition: The ruggedness of an analytical method is the degree of reproducibility of test results obtained by the analysis of the same samples under a variety of conditions, such as different laboratories, different analysts, different instruments, different days, etc.

Certain may Include

i. Source
ii. Concentration and stability of the solution
iii. Heating rate
iv. Column temperature
v. Humidity

9. Robustness

Definition: "The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, deliberate variations in method parameters and indicates its reliability during normal usage."

Determination

The evaluation of robustness should be considered during the development phase and depends on the type of procedure under study.

Variations may Include

- stability of the analytical solution
- variation of pH in a mobile phase
- different column (lot/supplier)
- temperature
- flow rate

10. System Suitability

- System suitability testing is an integral part of many analytical procedures.
- The tests are based on the concept that the equipment, electronics, analytical operations, and samples to be analyzed constitute an integral system that can be evaluated.

- USP has recommended system suitability testing in HPLC procedures

4.2 COMPUTERIZED SYSTEM VALIDATION

Computer systems installed in the corporations are validated to assure that:

1. 1.Systems are developed according to quality software engineering principles.
2. Systems meet the business needs of their users
3. Continue to operate correctly and reliably throughout their life cycle. we can say that CSV provides documented proof that the system (e.g., hardware, software, peripherals, and networks) will repeatedly and reliably do what it is designed to do, is "fit for purpose," and complies with the applicable rules and regulations

Regulatory Requirements

- In 1983, FDA published a guide to inspectComputerized Systems in Pharmaceutical Processing, also known as the 'bluebook' (FDA 1983).
- FDA introduced 21 CFR Part 11 for rules on usingelectronic records and electronic signatures (FDA 1997).
- Part 11 applies to electronic records and electronic signatures that persons create, modify, maintain, archive, retrieve, or transmit under any documents or signature requirement outlinedin the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act (PHS Act), or any FDA regulation.

What is 21 CFR Part 11?

21 CFR Part 11: Allow the industry to use electronic records and signatures alternatively to paper records and handwritten signatures

21 CFR Part 11 Applies

- To all FDA-regulated environments - When using computers in the creation, modification, archiving, retrieval, or transmission of data or records
- To records required by predicate rules – GLP, GCP, GMP – that impact patient safety.

Purpose of Part 11

- Ensure data is not corrupted or lost.
- Data is secure.
- Approvals cannot be repudiated(rejected).
- Changes to data can be traced.
- Attempts to falsify records are made difficult and can bedetected.

Part 11 electronic records

Electronic signatures:

Subpart A--General Provisions

11.1- Scope.

11.2 - Implementation.

11.3 - Definitions

Subpart B—Electronic Records

11.10 - Controls for closed systems.

11.30 - Controls for open systems.

11.50 - Signature manifestations.

11.70 - Signature/record linking.

Subpart C--Electronic Signatures

11.100 - General requirements.

11.200 - Electronic signature components and controls.
11.300 - Controls for identification codes/passwords

Scope

a) electronic records to be trustworthy, reliable, and generally equivalent to paper records.
b) records in electronic form that are created modified, maintained, archived, retrieved, or transmitted,
c) electronic signatures to be equivalent to complete handwritten signatures, initials, and other general signings, effective on or after August 20, 1997.
d) Electronic records may be used in lieu(instead) of paper records
e) Computer systems (including hardware and software)

Implementation

a) For records required to be maintained but not submitted to the agency.
b) For records submitted to the agency
c) The requirements of this part are met documents to be submitted have been identified in public docket No. 92S–0251

Definitions

- ***Agency*** means the Food and Drug Administration.
- ***Biometrics*** means verifying an individual's identity based on measuring the individual's physical feature(s) or repeatable action(s) where those features or actions are both unique to that individual and measurable.
- ***Closed system*** means an environment in which system access is controlled by persons responsible for the content of electronic records on the system.

- ***Digital signature*** means an electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such as the signer's identity.
- ***Electronic record*** means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.
- ***Open system*** means an environment in which system access at controlled by persons responsible for the content of electronic records on the system.

Controls for Closed Systems

Controls are designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records

a) Validation of systems
b) Accurate and complete copies
c) Protection of records by ready retrieval
d) Limiting system access
e) Audit trails
f) Operational system checks
g) Authority checks
h) Device (e.g., terminal) checks
i) Education, training, and experience
j) Written policies
k) Documentation

Distribution of, access, and system operation and maintenance.

Revision and change control.

a)Validation of systems

Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discover invalid or altered records.

b) Accurate and complete copies

The ability to generate accurate and complete copies of records in human-readable and electronic forms suitable for the agency's inspection, review, and copying.

Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.

c) Protection of records by ready retrieval

Protection of records to enable accurate and ready retrieval throughout the records retention period.

d) Limiting System Access

Limiting system access to authorized individuals

e) Audit Trails

- Use secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records.
- Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for at least as long as required for the electronic subject records. It shall be available for agency review and copying.

f) Operation Check

- Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.
- Empower 3 software uses Wizards to ensure proper sequencing.
- New Project Wizard
- Processing Method Wizard
- Sample Set Method Wizard
- Backup Project Wizard
- Restore Project Wizard

g) Authority Check

Use authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

h) Device Check

- Use of the device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.
- If the system requires that data input or instructions only come from specific input devices (e.g., instruments, terminals), does the system check for the correct device?

i*) Education, Training, and Experience*

Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.

j) Written Policies

- The establishment of/ adherence to written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures to determine record and signature falsification.
- Written policies shall be the party of user account open with user sign and statement "I am accountable and responsible for actions initiated under my electronic signature to determine record and signature falsification."

k) Documentation

Use of appropriate controls over systems documentation, including:

(1) Adequate controls over the distribution of access to, and user documentation for system operation and maintenance.

(2) Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation

- Distribution of access annexure
- System operation and maintenance log
- Revision procedure
- Change control procedure
- Audit trial with time-sequenced

Controls for Open Systems

- Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures andcontrols designed to ensure the authenticity, integrity, and, asappropriate, the

confidentiality of electronic records from thepoint of their creation to the end of their receipt.

- Such procedures and controls shall include those identified in § 11.10, as appropriate, and additional measures such asdocument encryption and use of applicable digital signaturestandards to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality.

Signature Manifestations

a) Signed electronic records shall contain information associated with the signing that indicates all of the following:

(1) The printed name of the signer;
(2) The date and time when the signature was executed;
(3) The meaning (such as review, approval, responsibility, or authorship) associated with the signature.

b) The items identified in paragraphs(a)(1), (a)(2), and (a)(3) of this section shall be subject to the same controls as for electronic records. They shall be included aspart of any human-readable form of the electronic record (such as an electronic display or printout).

Signature/Record Linking

Electronic and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

General requirements

1. Unique: Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.
2. Verify the identity: Before an organization establishes, assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature, the organization shall verify the individual's identity.
   - At the time of joining,the HR Department does the activity.
   - For vendor in service agreement need to be clarification.
3. Certify to the agency:Persons using electronic signatures shall, before or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.

1) The certification shall be submitted in paper and signed with a traditional handwritten signature to the Office of Regional Operations (HFC–100), 5600 Fishers Lane, Rockville, MD 20857.
2) Persons using electronic signatures shall, upon agency request, provide additional certification or testimony that a specific electronic signature is the legally binding equivalent of the signer'shandwritten signature.

For 11.2 Implementation. b) For records submitted to the agency

Electronic Signatures Components and Controls

a) Non-Biometric:Electronic signatures that are not based upon biometrics shall--

(1) Employ at least two distinct identification components: an identification code and password.

(i) When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be completed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is onlyexecutable by, and designed to be used only by, the individual.

(ii) When an individual executes one or more signings not performed during a single, continuous period of controlledsystem access, each signing shall be completed using all electronic signature components.

2) Be used only by their genuine owners;

3) Be administered and executed to ensure that attempted use ofan individual's electronic signature by anyone other than its genuine owner requires the collaboration of two or more individuals.

b) Biometric --Electronic signatures based upon biometrics shallbe designed to ensure that they cannot be used by anyone otherthan their genuine owners.

Controls for Identification Codes/ Passwords

Persons who use electronic signatures based upon identification codes and passwords shallemploy controls to ensure their security and integrity. Such controls shall include:

a) Uniqueness --Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same identification code and password combination.

b) Code and password Periodically Checked --Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).
c) Loss management --Following loss management procedures to electronically de-authorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous.
d) Safeguard to prevent unauthorized --Use of transaction safeguards to prevent unauthorized use of passwords and identification codes, and to detect and report immediately and urgently any attempts at their unauthorized use to the system security unit and, as appropriate, to organizational management.
e) Periodic testing of devices --Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function correctly and have not been altered in an unauthorized manner.

GAMP – Good Automated Manufacturing Practices

- It was founded in 1991 and is a trademark of the International Society for Pharmaceutical Engineering (ISPE).
- GAMP-5 was launched in 2008 and includes a set of procedures that help to ensure automation equipment/software meets required quality standards.
- Quality by design is a central principle of GAMP and advocates that quality is built into each stage of the manufacturing process.

- All aspects of production from the raw materials, facility, and equipment to the training and hygiene of staff are covered by

GAMP Recommendations

Although Good Automated Manufacturing Practice (GAMP) is not legislation, it's an essential guideline for companies involved in developing and implementing automated production systems.

GAMP Objectives

GAMP® guidance aims to achieve computerized systems that are fit for the intended use and meet current regulatory requirements by building upon existing industry good practicesefficiently and effectively.

Guidance

- It is not a prescriptive method or a standard but.
- Pragmatic guidance
- Approaches
- Tools for the practitioner
- Applied with expertise and good judgment

GAMP- Main Body Overview

- Key Concepts
- Life Cycle
- Quality Risk Management
- Regulated Company Activities
- Supplier Activities
- Efficiency Improvements

5 Key Concepts

- Life Cycle Approach Within a QMS
- Scaleable Life Cycle Activities
- Process and Product Understanding
- Science-Based Quality Risk Management
- Leveraging Supplier Involvement

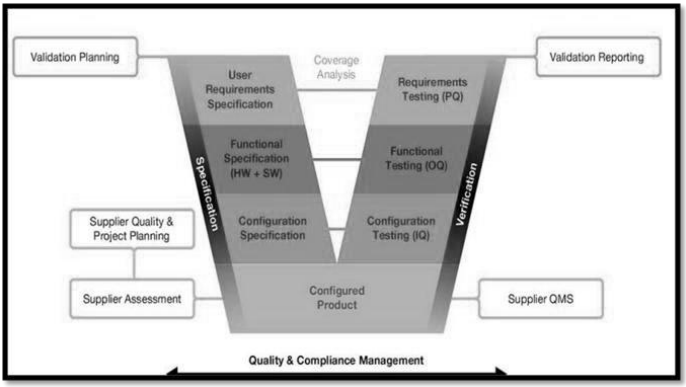
Product and Process Understanding

- Basis of science- and risk-based decisions
- Focus on critical aspects
  - Identify
  - Specify
  - Verify
- Critical Quality Attributes / Critical Process Parameters.

Life Cycle Approach Within a QMS

- Suitable Life Cycle.
- –Intrinsic to QMS
- Continuous improvement.
- Life cycle approach is fundamental to GAMP 5.

GAMP V Model Transition



Scaleable Life Cycle Activities

Scalability is based on --

- Risk
- Complexity and Novelty
- Supplier

Science-Based Quality Risk Management

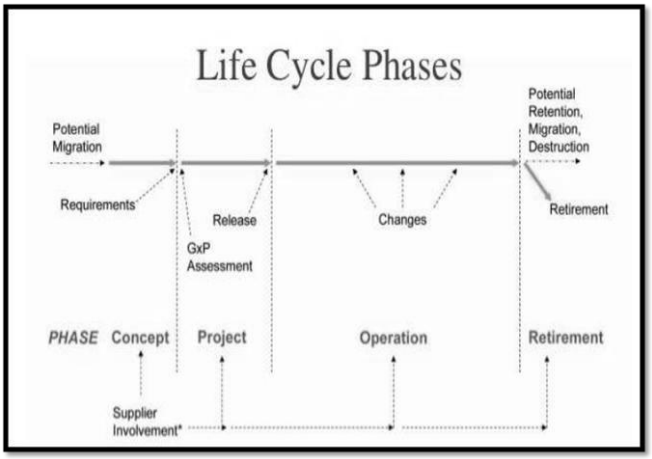
- Review Based on ICH Q9
- Assessment
- Control
- Communication
- Focus on patient
- Safety
- product quality
- data integrity

Leveraging Supplier Involvement Activities

- Requirements gathering
- Risk assessments
- Functional / other specifications
- Configuration
- Testing
- Support and maintenance

Principles

- Assess:
  - Suitability
  - Accuracy
  - Completeness
- Flexibility:
  - Format
  - Structure

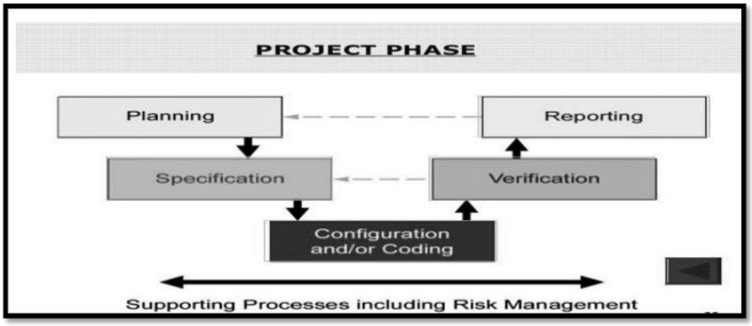


Compatibility with Other Standards

ASTM(American Society for Testing and Materials) E2500 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment.

Stages Within the Project Phase

- Planning
- Specification, configuration, and coding
- Verification
- Reporting and release.



Planning

- Activities
- Responsibilities
- Procedures
- Timelines

Specification, Configuration &Coding

- Specifications allow
  - Development
  - Verification
  - Maintenance
- Number and level of detail varies.
- Defined processes.

Verification

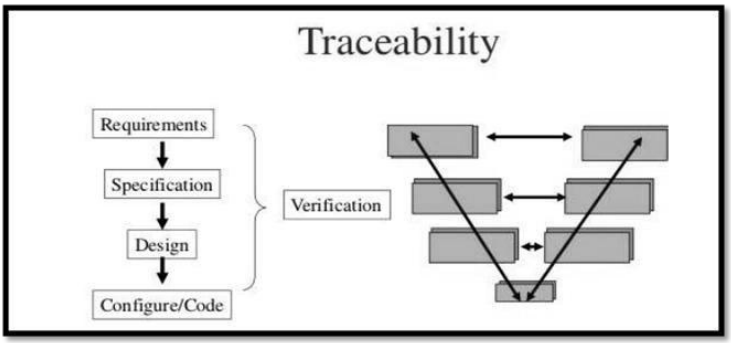
- Testing
- Reviews
- Identify defects

Supporting Processes

- Risk Management
- Change and Configuration Management
- Design Review
- Traceability
- Document Management

Design Review

- Planned
- Systematic
- Identify Defects
- Corrective Action
- Scaleable
  - Rigor/Extent
  - Documentation



GAMP 5 Categories

Category	GAMP 4	GAMP 5
1	Operating system	**Infrastructure software**
2	Firmware	No longer used
3	Standard software packages	**Non-configured products**
4	Configurable software packages	**Configured products**
5	Custom (bespoke) software	**Custom applications**

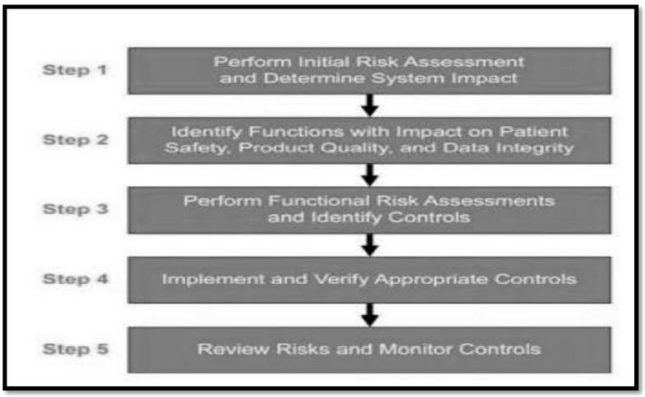
GAMP 5

Quality Risk Management Critical Processes

- Generate, manipulate, or control data supporting regulatory safety and efficacy submissions
- Control critical parameters in preclinical, clinical, development, and manufacturing
- Control or provide information for product release
- Control information required in case of a product recall
- Control adverse events or complaint recording or reporting

- Support pharmacovigilance

Five-step risk management approach



Step 1:Initial assessment

- An initial assessment should be performed based on understanding the business process.
- The understanding can be derived from user requirements, design specifications, operating procedures, regulatory requirements, and known functional areas.
- The assessment should include a decision on whether thesystem is GxP regulated and form an overall assessment of the system impact.

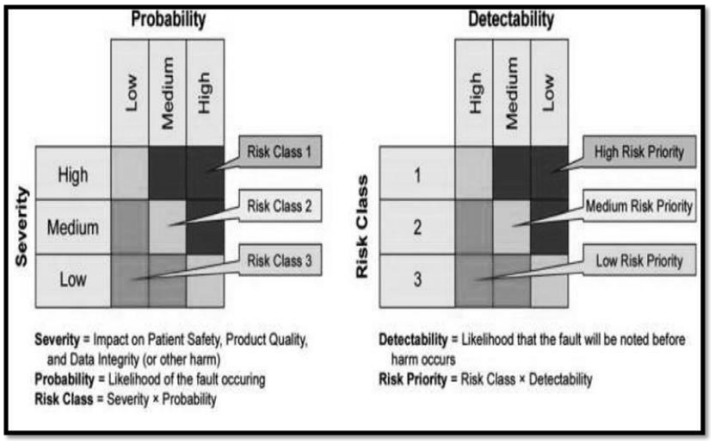
Step 2 – Identify Functions with Impact on Patient Safety, Product Quality, and Data Integrity

- Building upon the information obtained in Step 1, the specific functions that impact patient safety, product quality, and data integrity can be identified and addressed.

- It must be remembered that no function can be assessed as having a higher risk or impact than the process itself.

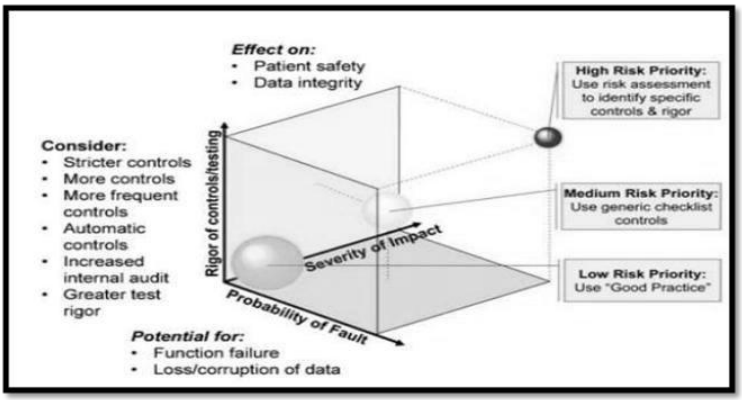
Step 3 – Perform Functional Risk Assessmentsand Identify Controls

- The functions identified in the previous step can now be analyzed by considering possible hazards and what controls may be needed to minimize potential harm.
- A company's risk tolerance is also a factor to be considered when selecting possible controls.



Step 4 – Implement and Verify Appropriate Testing and Controls

- Once the severity and risk are understood, the appropriate level of challenge testing can be selected.
- The concept of planning, testing, and selecting controls based on assessed risk and impact.



Step 5 – Review Risks and Monitor Controls

Once the controls are implemented, they need to be monitored. Implementing the controls may reduce the level of effort for many current activities, such as audits, assessments, documentation, testing, and even the degree of quality unit involvement.

UNIT-5
GENERAL PRINCIPLES OF INTELLECTUAL PROPERTY

Introduction

Intellectual Property Rights are legal rights, which result from intellectual activity in industrial, scientific, literary & artistic fields. These rights Safeguard creators and other producers of intellectual goods & services by granting them certain time-limited rights to control their use. Protected IP rights like other property can be a matter of trade, which can be owned, sold or bought. These are intangible and non-exhausted consumption.

Basic Concept in IPR

- Intellectual property is an intangible creation of the human mind, usually expressed or translated into a tangible form that is assigned certain rights of property.
- Examples of intellectual property include an author's copyright on a book or article, a distinctive logo design representing a soft drink company and its products, unique design elements of a web site, or a patent on the process to manufacture chewing gum.
- Intellectual property rights (IPR) can be defined as the rights given to people over the creation of their minds. They usually give the creator an exclusive right over the use of his/her creations for a certain period of time.
- Intellectual property (IP) refers to creations of the mind: inventions, literary and artistic works, and

symbols, names, images, and designs used in commerce.

Objectives of IPR

- Intellectual property Right (IPR) is a term used for various legal entitlements which attach to certain types of information, ideas, or other intangibles in their expressed form.
- The holder of this legal entitlement is generally entitled to exercise various exclusive rights in relation to the subject matter of the Intellectual Property.
- The term intellectual property reflects the idea that this subject matter is the product of the mind or the intellect, and that Intellectual Property rights may be protected at law in the same way as any other form of property.
- Intellectual property laws vary from jurisdiction to jurisdiction, such that the acquisition, registration or enforcement of IP rights must be pursued or obtained separately in each territory of interest.
- Intellectual property rights (IPR) can be defined as the rights given to people over the creation of their minds. They usually give the creator an exclusive right over the use of his/her creations for a certain period of time.

Types of IPR

- Patents
- Trademarks
- Copyrights and related rights
- Geographical indications
- Industrial designs
- Trade secrets

- Layout design for integrated circuits
- Protection of new plant variety

Patents

A patent is an exclusive right granted for an invention, which is a product or a process that provides a new way of doing something, or offers a new technical solution to a problem. It provides protection for the invention to the owner of the patent. The protection is granted for a limited period, i.e. 20 years. Patent protection means that the invention cannot be commercially made, used, distributed or sold without the patent owner's consent. A patent owner has the right to decide who may - or may not - use the patented invention for the period in which the invention is protected. The patent owner may give permission to, or license, other parties to use the invention on mutually agreed terms. The owner may also sell the right to the invention to someone else, who will then become the new owner of the patent. Once a patent expires, the protection ends, and an invention enters the public domain, that is the owner no longer holds exclusive rights to the invention, which becomes available to commercial exploitation by others. All patent owners are obliged, in return for patent protection, to publicly disclose information on their invention in order to enrich the total body of technical knowledge in the world. Such an ever-increasing body of public knowledge promotes further creativity and innovation in others. In this way, patents provide not only protection for the owner but valuable information and inspiration for future generations of researchers and inventors

What Can Be Patented

Product, Process, Machine, Manufacture, Composition of Matter.

Trademarks

A trademark is a distinctive sign that identifies certain goods or services as those produced or provided by a specific person or enterprise. It may be one or a combination of words, letters, and numerals. They may consist of drawings, symbols, three- dimensional signs such as the shape and packaging of goods, audible signs such as music or vocal sounds, fragrances, or colours used as distinguishing features. It provides protection to the owner of the mark by ensuring the exclusive right to use it to identify goods or services, or to authorize another to use it in return for payment. It helps consumers identify and purchase a product or service because its nature and quality, indicated by its unique trademark, meets their needs.

Registration of trademark is prima facie proof of its ownership giving statutory right to the proprietor. Trademark rights may be held in perpetuity. The initial term of registration is for10 years; thereafter it may be renewed from time to time.

Copyrights and Related Rights

Copyright is a legal term describing rights given to creators for their literary and artistic works. The kinds of works covered by copyright include: literary works such as novels, poems, plays, reference works, newspapers and computer programs; databases; films, musical compositions, and choreography; artistic works such as paintings, drawings, photographs and sculpture; architecture; and advertisements, maps and technical drawings. Copyright subsists in a work by

virtue of creation; hence it's not mandatory to register. However, registering a copyright provides evidence that copyright subsists in the work & creator is the owner of the work. Creators often sell the rights to their works to individuals or companies best able to market the works in return for payment. These payments are often made dependent on the actual use of the work, and are then referred to as royalties. These economic rights have a time limit, (other than photographs) is for life of author plus sixty years after creator 's death.

Geographical Indications

GI are signs used on goods that have a specific geographical origin and possess qualities or a reputation that are due to that place of origin? Agricultural products typically have qualities that derive from their place of production and are influenced by specific local factors, such as climate and soil. They may also highlight specific qualities of a product, which are due to human factors that can be found in the place of origin of the products, such as specific manufacturing skills and traditions. A geographical indication points to a specific place or region of production that determines the characteristic qualities of the product that originates therein. It is important that the product derives its qualities and reputation from that place. Place of origin may be a village or town, a region or a country. It is an exclusive right given to a particular community hence the benefits of its registration are shared by the all members of the community. Recently the GIs of goods like Chanderi Sarees, Kullu Shawls, and Wet Grinders etc have been registered. Keeping in view the large diversity of traditional products spread all over the country, the registration under GI will be very important in future

growth of the tribes / communities / skilled artisans associated in developing such products.

Industrial Designs

Industrial designs refer to creative activity, which result in the ornamental or formal appearance of a product, and design right refers to a novel or original design that is accorded to the proprietor of a validly registered design. Industrial designs are an element of intellectual property. Under the TRIPS Agreement, minimum standards of protection of industrial designs have been provided for. As a developing country, India has already amended its national legislation to provide for these minimal standards. The essential purpose of design law it to promote and protect the design element of industrial production. It is also intended to promote innovative activity in the field of industries. The existing legislation on industrial designs in India is contained in the New Designs Act, 2000 and this Act will serve its purpose well in the rapid changes in technology and international developments. India has also achieved a mature status in the field of industrial designs and in view of globalization of the economy, the present legislation is aligned with the changed technical and commercial scenario and made to conform to international trends in design administration. This replacement Act is also aimed to enact a more detailed classification of design to conform to the international system and to take care of the proliferation of design related activities in various fields.

Trade Secrets

It may be confidential business information that provides an enterprise a competitive edge may be considered a trade secret. Usually these are manufacturing or industrial secrets and commercial secrets. These include sales methods,

distribution methods, consumer profiles, and advertising strategies, lists of suppliers and clients, and manufacturing processes. Contrary to patents, trade secrets are protected without registration. A trade secret can beprotected for an unlimited period of time but a substantial element of secrecy must exist, so that, except by the use of improper means, there would be difficulty in acquiring the information. Considering the vast availability of traditional knowledge in the country the protection under this will be very crucial in reaping benefits from such type of knowledge. The Trades secret, traditional knowledge are also interlinked / associated with the geographical indications.

Layout Design for Integrated Circuits

Semiconductor Integrated Circuit means a product having transistors and other circuitry elements, which are inseparably formed on a semiconductor material or an insulating material or inside the semiconductor material and designed to perform an electronic circuitry function. The aim of the Semiconductor Integrated Circuits Layout Design Act 2000 is to provide protection of Intellectual Property Right (IPR) in the area of Semiconductor Integrated Circuit Layout Designs and for matters connected therewith or incidental thereto. The main focus of SICLD Act is to provide for routes and mechanism for protection of IPR in Chip Layout Designs created and matters related to it. The SICLD Act empowers the registered proprietor of the layout-design an inherent right to use the layout-design, commercially exploit it and obtain relief in respect of any infringement. The initial term of registration is for 10 years; thereafter it may be renewed from time to time. Department of Information Technology Ministry of Communications and Information Technology is the

administrative ministry looking after its registration and other matters.

Protection of New Plant Variety

The objective of this Act is to recognize the role of farmers as cultivators and conservers and the contribution of traditional, rural and tribal communities to the country's agro biodiversity by rewarding them for their contribution and to stimulate investment for R & D for the development new plant varieties to facilitate the growth of the seed industry. The Plant Variety Protection and Farmers Rights act 2001 was enacted in India to protect the New Plant Variety; the Act has come into force on 30.10.2005 through Authority. Initially 12 cropspecies have been identified for regt. i.e. Rice, Wheat, Maize, Sorghum, Pearl millet, Chickpea, Green gram, Black gram, Lentil, Kidney bean etc. India has opted for sui- generic system instead of patents for protecting new plant variety. Department Agriculture and Cooperation is the administrative ministry looking after its registration and other matters.

Concept Related Patents

1. Types of Patent

Utility Patent

- If you have a new, useful invention that is not obvious to others in the field of invention, you may qualify for a utility patent. Utility patents are grouped in five categories: a process, a machine, a manufacture, a composition of matter, or an improvement of an existing idea.
- Often, an invention will fall into more than one of the categories. For instance, computer software can usually be described both as a process (the steps that it

takes to make the computer do something) and as a machine (a device that takes information from an input device and moves it to an output device).

- Regardless of the number of categories in which an invention falls, only one utility patent may be issued on it.
- Among the many types of creative works that might qualify for a utility patent are biological inventions; new chemical formulas, processes, or procedures; computer hardware and peripherals; computer software; cosmetics; electrical inventions; electronic circuits; food inventions; housewares; machines; and magic tricks. If you acquire a utility patent, you can stop others from making, using, selling and importing the invention.
- A utility patent last for 20 years from the date that the patent application is filed.

Design Patent

- If you create a new and original design that ornaments a manufactured device, you may qualify for a design patent.
- Design patents are granted for any new or original Ornamental design for an article of manufacture. A design patent protects only the appearance of the article and not the article itself. An inventor can easily register both a utility patent and a design patent.
- A design patent is granted for product designs—for example, an IKEA chair, Keith Haring wallpaper, or a Manolo Blahnik shoe. You can even get a design patent for a computer screen icon. There are strings attached to a design patent, too.

- As noted, the design must be ornamental or aesthetic; it can't be functional. Once you acquire a design patent, you can stop others from making, using, selling and importing the design. You can enforce your design patent for only 14 years after it's issued.

Plant Patent

- The least-frequently issued type of patent are plant patents—granted for any asexually or sexually reproducible plants (such as flowers) that are both novel and nonobvious.
- This may include cultivating different types of plants to create mutants or hybrids and also newly found seedlings. This patent protects the owner by keeping other individuals or businesses from creating the type of plant or profiting from the plant for at least 20 years from the date of the application

2. Tangible and Intangible Property

Property is an external thing that can be owned or possessed. Property can be divided into two categories: tangible and intangible. The word tangible refers to something that has a definable physical form that can be felt or touched. The word intangible refers to something that cannot be perceived by the senses.

Tangible Property

In law is, literally, anything which can be touched, and includes both real property (or, in civil law systems, immovable property) and personal property (or moveable property), and stands in distinction to intangible property. In English law and some Commonwealth legal systems, items of tangible property are referred to as choses in possession (or a

chose in possession in the singular). However, some property, despite being physical in nature, is classified in many legal systems as intangible property rather than tangible property because the rights associated with the physical item are of far greater significance than the physical properties. Principally, these are documentary intangibles. For example, a promissory note is a piece of paper that can be touched, but the real significance is not the physical paper, but the legal rights which the paper confers, and hence the promissory note is defined by the legal debt rather than the physical attributes. A unique category of property is money, which in some legal systems is treated as tangible property and in others as intangible property. Whilst most countries legal tender is expressed in the form of intangible property ("The Treasury of Country X hereby promises to pay to the bearer on demand...."), in practice bank notes are now rarely ever redeemed in any country, which has led to bank notes and coins being classified as tangible property in most modern legal systems. Tangible property consists of real property and personal property. Real property is property that does not move, such as land and the things that are attached to or built on that land. Personal property is property that can be moved or any other tangible property that can be owned. Personal property is also called chattels. Chattels that are attached to the land and that cannot be removed without damaging the land are called fixtures. Examples of fixtures are built-in bookcases and ceiling fans.

Intangible Property

Intangible property consists of property that lacks a physical existence. Examples of intangible property include checking and savings accounts, options to buy or sell shares of stock, the goodwill of a business, a patent, and spousal love

and affection. Also known as incorporeal property, describes something which a person or corporation can have ownership of and can transfer ownership of to another person or corporation, but has no physical substance. It generally refers to statutory creations such as copyright, trademarks, or patents. It excludes tangible property like real property (land, buildings and fixtures) and personal property (ships, automobiles, tools, etc.). In some jurisdictions intangible property are referred to as choses in action. Intangible property is used in distinction to tangible property.

It is useful to note that there are two forms of intangible property - legal intangible property (which is discussed here) and competitive intangible property (which is the source from which legal intangible property is created but cannot be owned, extinguished, or transferred). Competitive intangible property disobeys the intellectual property test of voluntary extinguishment and therefore results in the sources that create intellectual property (knowledge in its source form, collaboration, process-engagement, etc) escaping quantification. Generally, ownership of intangible property gives the owner a set of legally enforceable rights over reproduction of personal property containing certain content. For example, a copyright owner can control the reproduction of the work forming the copyright.

However, the intangible property forms a set of rights separate from the tangible property that carries the rights. For example, the owner of a copyright can control the printing of books containing the content, but the book itself is personal property which can be bought and sold without concern over the rights of the copyright holder. In English law and other Commonwealth legal systems, intangible property is traditionally divided in pure intangibles (such as debts, intellectual property rights and goodwill) and documentary

intangibles, which obtain their character through the medium of a document (such as a bill of lading, promissory note or bill of exchange). The recent rise of electronic documents has blurred the distinction between pure intangibles and documentary intangibles.

Factor Affecting on Intellectual Property

Term of market exclusivity	Market exclusivity provided by regulatory approval Extensions for pediatric investigation Extensions for orphan drugs
Patentability standards	Utility/industrial applicability Novelty (and grace periods)Priority rules
Trademarks	Protection of brand names Protection of "trade dress"
Copyright	Marketing/training materials
Database protection	Proprietary collections/linking of physical, genomic, epidemiological data

Penalites For Violation

Intellectual Property Rights are the legal rights that are granted to a person for any creative and artistic work, for any invention or discovery, or for any literary work or words, phrases and symbols or designs for a stipulated period of time.

Intellectual property is any innovation, commercial or artistic, or any unique name, symbol, logo or design used commercially. In India, Intellectual Property is governed under the Patents Act, 1970; Trademarks Act, 1999; Copyright Act 1957; Designs Act, 2001, etc.

Intellectual Property Rights are the legal rights that are granted to a person for any creative and artistic work, for any

invention or discovery, or for any literary work or words, phrases and symbols or designs for a stipulated period of time.

The owners of Intellectual Property are granted certain exclusive rights through which they use their property without any disturbance and can prevent the misuse of their property.

Intellectual property is any innovation, commercial or artistic, or any unique name, symbol, logo or design used commercially. In India, Intellectual Property is governed under the Patents Act, 1970; Trademarks Act, 1999; Copyright Act,1957; Designs Act, 2001, etc.

Infringement

Infringement is breach or the contravention of the prescribed procedure of the law. When a person acts ultravires, it becomes a breach of law which ultimately results in violation or infringement of law. Infringement is described as "a crime less serious than a felony."

Infringement of Intellectual Property

- The use of intellectual property by a stranger without the prior consent of the owner is infringement of intellectual property.
- The infringement of Intellectual Properties includes Patent Infringement, Trademark Infringement, Copyright Infringement, etc.

Patent Infringement

- A person can use a patented product by seeking permission from the owner. This permission may typically be granted in the form of a license.

- In case of India, the patent infringement proceedings can be initiated only after the grant of patent. Persons involved in making, using, selling, distributing, importing or offering any of the above may be held liable for infringement.

Trade Mark Infringement

It is a violation of exclusive rights attaching to a trademark without the authorization of the trademark owner or licensees (provided that such sanction was within the scope of the license). Infringement may occur when one party, the "infringer", uses a trademark which is identical or confusingly similar to a trademark owned by other party, in relation to products or services which are identical or similar to the products or services which the registration covers.

Copyright Infringement

Copyright infringement or copy right violation is the unauthorized use of material that is covered by copyright law, in a manner that violates one of the copy right owner's exclusive rights, such as the right to reproduce or perform the copyrighted work, or to make derivative works. For electronic and audio visual media, unauthorized reproduction and distribution is occasionally referred to as piracy The true test to determine infringement is when a trader, spectator or viewer after having read or seen both the works should get an unmistakable impression that the subsequent work appears to be a copy of the first.

Remedies Available for Infringement

When there is a violation or an infringement of an intellectual property, it becomes the sole right of the Intellectual property holder to obtain a remedy for the

infringement of something that he has acquired with a lot of hard work and tremendous efforts.

Patent Infringement Remedies

- A Suit for Infringement of Patent has to be filed before the District Court or the High Court (depending on the pecuniary jurisdiction) within whose territorial jurisdiction the cause of action has arisen. However if the counter claim for revocation has been filed against the same, only the High Court has the jurisdiction to entertain the matter. The right to move the court of law t o rights
- The reliefs that a court may grant in a patent infringement suit, would include an injunction and, at the option of the plaintiff either damages or an account of profits. The court may also order that the goods which are found to be infringing and materials and implement, the predominant use of which is in the creation of infringing goods shall be seized, forfeited or destroyed, as the court deems fit under the circumstances of the case without payment of any compensation

Trademark Infringement Remedies

- An owner of a Trademark may commence legal proceedings against a party which infringes its registration
- A Suit for Infringement has to be filed before the District Court or the High Court (depending on the pecuniary jurisdiction) within whose territorial jurisdiction the cause of action has arisen.
- The Criminal Remedies available are that a suit for the above offences can be filed before the magistrate

within whose territorial jurisdiction the offence is committed or Police can register an FIR and prosecute directly; (statutory requirement to obtain the Registrar's approval).

Copyright Infringement Remedies

- A Suit for Infringement of copyright has to be filed in a District Court or a High Court (depending on the pecuniary jurisdiction) within whose territorial jurisdiction the cause of action has arisen.
- There are also Administrative Remedies available to the copyright, trademark and patent which include ban of import or export of goods including protection of patents, trademarks and copyrights confiscation of infringing material by Excise Authorities and delivery to the owner and Restrictions against parallel importation of goods

Role of IP in Pharmaceutical Industry

The pharmaceutical industry is one of the evergreen industries in the world. No matter what happens, whether the economy is on its most stable behavior or in recession mode. Any day a person can fall sick or might require his supplement pills. Basically the products are used 24/7.

Importance

Protection of Invention

You have designed or developed a drug and you need to protect it or else it is going to be stolen from you. So the way to protect is either by getting it patented or under trade secret. The problem with trade secret is that it the drug can be reverse engineered and hence your invention can be stolen. Whereas patent provides a much more water tight protection.

Economic Growth and Competitiveness

IPR is very important for economic growth of a company. Awarding sole rights to the inventor gives him the privilege of reaping the profits without any division. The marketing rights over the product are solely the inventors and he can sell it or license it. The company can earn a lot and reinvest it. Investing in research and development is very important for a company as it has to stay in the forefront.

Protects Consumers and Families

IPR's main interest lies in public safety. Protection and safety of public is always given importance. IPR helps the consumer in making the right choice when selecting a product. IPR helps in ensuring a standard and assures quality which helps the consumer make his choice and puts him at ease

Generate Solutions to Global Challenges

Promoting innovation is very important but at the same time you need funding to do it. IPR gives you the right encouragement to do it. There is a need for developing new drugs and vaccines as there are new diseases being discovered daily or there is resistance development by the pathogen.

Encourage Innovation and Reward Entrepreneurs

It is very important that the right push is given for inventors to keep them motivated. It is also important that they are recognized for their work. IPR gives them this encouragement. It enables a free flow of information by enabling a safe environment. When you know it is safe to share your invention then there is going to be a safe channel for exchange

Filing a Patent Applications, Patent Application Forms & Guidelines

Filing a patent application in the Indian Patent Office is the first step towards securing a patent to your invention in India. To file a patent application, a set of forms has to be submitted to the patent office. The forms can be submitted online (http://ipindiaonline.gov.in/epatentfiling/goForLogin/doLogin) if you have a class 3 digital certificate. Alternatively, you can send true copies (hard copies) to the patent office. The patent office charges a 10% additional fee if applications are filed offline.

Please note that preparing a patent specification is essential in filing a patent application. Drafting a patent specification is a highly skilled job, which can only be performed by persons with both technical and patent law expertise. Therefore, if a person or company is serious about protecting their intellectual property, it is highly recommended to use the services of professional patent practitioners. To know more about this, you can read our article on this:

Why should patent professionals draft patent specifications?

Further, we have provided this article for knowledge purposes only. It is recommended to avail services of professionals to file patent applications, as mistakes will prove costly. A thorough understanding of the Indian Patent Act is essential for filing patent applications. Patent agents understand the Indian Patent Act and are the only persons (other than the applicant themselves) authorized by the Patent Office to file patent applications on behalf of the applicant. InvnTree employs patent agents.

Indian patent offices are in Delhi, Kolkata, Mumbai, and Chennai. Therefore, the patent application must be filed in the appropriate office based on your/your company's location.

Once you have identified the patent office in which you have to file your patent application, it is time to get an overview of the forms that must be submitted.

To file a patent application, you will have to submit forms 1, form 2, form 3 and form 5. Subsequent to filing these forms with the appropriate fees, you will receive a patent application number from the patent office. You can choose to file form 9 (optional) and form 18 along with filing a complete application or after filing a complete application. You can download the Indian patent application filing forms.

The table below provides the list of forms that must be submitted and their respective fees. Please note that the cost mentioned is for E-filing only. The patent office charges an additional fee of 10% over the payment for applications filed offline.

Form	Title	Patent office Fee (INR) 1$ = ~ 60 INR E-Filing only			Comment
		Applicant- Natural person/ Startup	Applicant – other than natural person		
			Small Entity	Others except small entity	
1	Application for Grant of Patent	1600	4000	8000	Mandatory
2	Provisional/Complete Specification	No fee*	No fee*	No fee*	Mandatory
3	Statement and Undertaking Under Section 8	No fee	No fee	No fee	Mandatory
5	Declaration as to Inventorship	No fee	No fee	No fee	Mandatory
9	Request for Publication	2500	6250	12500	Optional
18	Request for Examination of Application for Patent	4000	10000	20000	Mandatory

Based on the type of applicant, a fee of 160/400/800/sheet is applicable for each sheet exceeding 30 sheets in a patent specification. Further, an INR 320/800/1600/Claim fee, based on the applicant type, is applicable for each claim exceeding ten claims in the patent specification.

An overview of each of the forms is provided below.

Form 1 – Application for Grant of Patent

As the name suggests, this form is an application for a grant of patent in India. Therefore, in this form, you will have to furnish information, such as the name and address of the inventor(s), the name and address of the applicant(s), information corresponding to prior patent applications relating to the current invention, which you or any authorized

entity has filed, and some declarations, among other information.

(Added after receiving comments from Mr. Naren) Please note that a local communication address (address in India) has to be provided. This point is of importance to foreign (Non-Indian) applicants.

Form 2 – Provisional/Complete Specification

Form 2 is used to furnish your patent specification. The patent specification can be provisional or a complete patent specification, depending on the type of patent application (provisional or complete) you are filing. You might find our article "What are the different patent filing options?" helpful.

If you are filing a provisional patent application, then use the following preamble on the first page of Form 2:

The following specification describes the invention

On the other hand, if you are filing a complete patent application, then use the following preamble on the first page of Form 2:

The following specification mainly describes the invention and how it is to be performed

Note that if you are filing offline, two copies of the patent specification must be sent to the patent office. Additionally, count the number of sheets and claims (extra fee for more than 30 sheets and more than ten claims) and calculate the appropriate fee. While counting the sheets, even the drawing sheets will have to be considered.

Form 3 – Statement and Undertaking Under Section 8

Form 3 is used to furnish information/actions relating to patent applications filed in other countries for the current

invention. Additionally, any information pertaining to the rights corresponding to the present patent application has to be furnished. Further, you would be using form 3 to undertake that you will be keeping the patent office informed in writing the details regarding corresponding applications for patents filed outside India. You can read more about this in our article.

Form 5 – Declaration as to Inventorship

This application is used to declare the inventors of the subject matter sought to be protected using the current patent application.

Form 9 – Request for Publication

If this form is not filed, the patent specification will be published by the patent office after 18 months from the priority date (Filing of the first patent application for the current subject matter). On the other hand, by filling out this form, you can generally have your patent specification published within one month from filing this form. Note that the patent rights start from the date of publication of the patent application (enforceable after the grant).

Form 18 – Request for Examination of Application for Patent

This form can be filed within 48 months from the priority date. The patent office will not consider your application for examination unless this form is filed. Hence, if you wish to expedite the patenting process, filing form 9 and 18 at an early stage is advised. A startup can also request for expedited examination of their patent application. The fee for this is INR 8000. Currently, the patent office has limited this request to about 1000 requests in a year.

Types of Patent Application

A patent is a statutory authorization or licenses establishing a right or title over an invention for a particular period. It primarily means preventing other businesses of its kind from making, using, or selling an invention of a similar nature.

Patent Application

A patent application is a plea to grant a patent for the invention described and claimed by the applicant. An application for this purpose generally comprises a description of the invention, with official forms and correspondence relevant to the application. Patent applications are of several types, each of which caters to a unique purpose.

Types of Patent

The types of the patent application are:

- Provisional Application
- Ordinary or Non-Provisional Application
- Convention Application
- PCT International Application
- PCT National Phase Application
- Patent of Addition
- Divisional Application

The rest of the article covers these types in detail.

Provisional Application

A provisional application, also known as a temporary application, is filed when an invention is under experimentation and isn't finalized. Moreover, it is a preliminary application filed before the patent office for claiming priority, as the Indian Patent Office follows the 'First to the File system (known popularly as the First-Come-First-

Served-Basis). In technical terms, the early Filing of an invention will prevent the occurrence of any other related inventions from being designated as prior art to the inventor's application.

Add more, and this patent application is filed when an invention requires additional time for development. For example, if a provisional specification supports an application, the applicant is necessitated to file a complete specification within twelve months from the date of filing a provisional application. A failure in this part would render the application void.

An application for this purpose must include a brief explanation of the invention. It must be drafted meticulously to ensure that the priority rights are secured for the invention.

Ordinary or Non-Provisional Application

This type of application is filed if the applicant doesn't have any priority to claim or if the application is not filed in pursuance of any preceding convention application. In addition, it must be supported by a complete specification that depicts the invention in detail.

The complete specification can be filed through:

Direct Filing – wherein complete specification is initially filed with the Indian Patent Office without filing any corresponding provisional specification.

Subsequent Filing – the wherein complete specification is filed after filing the corresponding provisional specification and claiming priority from the filed provisional specification.

A complete specification entails the following:

Title

A preamble to the invention.

The technical field of the invention.

Background of the invention.
Objects of the invention.
Statement of the invention.
A brief description of the drawings
A detailed description of the invention.
Claims
Abstract

Convention Application

A convention application is filed for claiming a priority date based on the same or substantially similar application filed in any of the convention countries. To avail of a status of convention, an applicant must apply to the Indian Patent Office within a year from the date of the initial Filing of a similar application in the convention country. To re-iterate in simpler terms, a convention application entitles the applicant to claim priority in all the convention countries.

PCT International Application

As can be deciphered from its name, a PCT Application is an international application. Though the application does not provide for the grant of an international patent, it paves the way for a streamlined patent application process in many countries in one go. It is governed by the Patent Corporation Treaty and can be validated in up to 142 countries. Filing this application would protect an invention from being replicated in these designated countries.

Unlike other applications, it renders the application a time frame of 30-31 months to enter into various countries from the international filing date or the priority date, thereby affording the applicant additional time to access the invention's viability.

Apart from this, it renders the following other benefits:

The application provides an International Search Report citing prior art, which discloses whether or not the invention is novel. It gives an option for requesting an International Preliminary Examination Report, which is a report that contains an option on the patentability of the invention.

The reports above facilitate the applicant to make more informed choices early in the patent process, as they can amend the application to deal with any conflicting material. Also, the applicant would receive a glimpse of the invention's patentability before incurring charges for filing and prosecuting the application in each country.

An applicant from India can file this application at:

The Indian Patent Office (IPO) acts as the receiving office.

The International Bureau of WIPO, either after availing a foreign filing permit from IPO or after six weeks and 12 months of applying in India.

PCT National Phase Application

It is considered essential for an applicant to file a national phase application in each country where protection is sought. The time frame for filing the same is scheduled within 31 months from the priority date or the international filing date, whichever is earlier. The time limit could be enhanced through National Laws by each member country.

Concerning the National Phase Application, the title, description, abstract and claims as filed in the International Application under PCT shall be considered the Complete Specification. Apart from this, the regulations for filing and processing an ordinary patent application are also applied here.

Patent of Addition

This application must be filed if the applicant discovers that he has come across an invention which is a slight modification of the invention that has already been applied for or patented by the applicant. It can only be filed if the invention doesn't involve a substantial inventive step.

A patent of addition is only granted after the grant of the parent patent; hence, no separate renewal fee should be remitted during the term of the main patent. Moreover, it shall be granted for a term equal to that of the patent for the primary invention and therefore expires along with the main patent. The filing date here shall be the date on which the application for patent of addition has been filed.

Divisional Application

An applicant may divide an application and furnish two or more applications if a particular application claims for more than one invention. The priority date for these applications is similar to that of the parent application.

International Patenting Requirements Procedure and Cost

After deciding which route to follow in filing an international application, an international application can be prepared. We now summarize the general procedures for filing directly or using the PCT.

To file a patent application directly in different countries, the rules and procedures of the individual countries must be followed.

Generally, the following steps are necessary to file an international application directly:

(1) Fill in the form(s) required by that office;
(2) Pay the fees for each application in foreign currencies;
(3) Meet the formality standards set by each country;

(4) Provide an address for service in each country;
(5) If required, provide a translation into the local language;
(6) Provide a description — including drawings, if necessary;
(7) Provide a claim or claims; and
(8) Provide a certified copy of the foreign application if claiming priority.4

Filing a PCT application generally has two phases: international and national.

Each of these phases is discussed in turn below.

International Phase: In the international phase, the PCT application is filed with

WIPO. Generally, to file a PCT application, the following steps are taken:

(1) Fill in a PCT Request form or lodge your application electronically using PCT-SAFE;
(2) Pay the relevant PCT fees in domestic currency;
(3) Provide a description — including drawings, if necessary;
(4) Provide a claim or claims;
(5) Provide a certified copy of the foreign application if claiming priority;
(6) International search carried out;
(7) International search report and written opinion produced;
(8) Application published 18 months from earliest priority date;
(9) International Preliminary Examination is requested (optional); and
(10) Establish an International Preliminary Report on Patentability at 30 months. If no demand is requested.

Table 1 below summarizes the International Phase.

Stage One The PCT application is filed	The Receiving Office (RO) checks the application for mistakes. The RO then assigns the application a filing number.	This part of the process usually takes sixto eight weeks.
Stage Two An International Search is carried out	An international search is carried out by the International Search Authority (ISA) to look for any relevant documents describing similar inventions related to the one you have described in your PCT application. The findings of the search are compiled in a search report called an International Search Report (ISR). An examination report called a Written Opinion of the International Searching Authority (ISO) is	As a PCT requirement, the ISR andISO must be issued within three months of the application's lodgment date or nine months of the earliest priority date, whichever is later.

	also	
	Considering that there are still deficiencies in your application, you will be givena Written Opinion (IPO); otherwise, the examiner will establish an International Preliminary Report on Patentability (Chapter II) (IPRPII). The IPEO, like the ISO, explains why documentshave been cited and alert you to any problems your application may have concerning novelty, inventiveness, and industrial applicability, as well as anyproblems of clarity in your specification. You can then file amendments to your application when filing the demand or in response to an IPEO any timeup to	

	the establishment of theIPRPII. Please note – the decision on granting a patentremains the task of the national or regional offices where you enter the nationalphase — the IPRPII is authoritative. Still, it is not binding in these offices.	
	Produced. These reports are sent to your agent and the IB. You can amend your claims (under Article 19 — see *In more depth*) based on your ISR and ISO findings – amendments must be made within two months of receiving the ISR and ISO or within 16 months of the earliest priority date.	
Stage Three The IB publishes the application	There is no provision for the delay in publishing the application — it can	Eighteen months from the earliest priority date,the IB publishes the

	be published without the completed ISR if necessary. At this point, if the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application or the priority claim must reach the IB before the completion of the technical preparations for international publication —this must be done no laterthan 15 working days beforeit is published.	application and the ISR. At 30 months from the earliest prioritydate, the IB uses the ISOto establish the IPRP1, which is communicated to all designated offices.
Stage Four — Optional An International Preliminary Examinationis requested	You can request an optional International Preliminary Examination (IPE) of the application —this request is called demand. The IPE is based on the ISO and any amendmentsyou file and helps you refine your application	The examiner must, in any event, establish the IPRPII by28 months after the earliest priority date. This will be an adversereport if you have not overcome all deficiencies.

	before you decide to proceed with the national phase. If you have requested an IPE and the international preliminary examiner	

Are Patents Protected Internationally?

A Patent is a territorial right. It is applicable in a particular country in which a patent is registered. Generally, different countries have different rules and regulations regarding Patent protection. Moreover, there is no concept of international patent protection. But the following are the three ways to protect an invention in different countries:

1. Direct Registration

One can submit separate national patent applications in each country to get a patent for an invention. Additionally, different countries will grant patents separately per their rules and regulations. Therefore, the processing fee will vary from country to country, and you have to pay a separate fee for every patent application.

2. Paris Convention

The Paris Convention allows inventors to file a first patent application for the Protection of Industrial Property in their home country. This application is the priority document for filing patent applications in other Paris Convention states. Further, there are 170+ Member States of the Paris Convention. Therefore, one should apply within 12 months from the filing date of that first patent application. Further, if

the countries or regions an applicant wants to apply to are 1-3 countries, prefer this way.

3. Patent Cooperation Treaty

The Patent Cooperation Treaty (PCT) is an international treaty with more than 150 States. The World Intellectual Property Organisation (WIPO) regulates PCT.

The PCT is the worldwide accepted system that makes the Patent application process easy in different nations. Further, there is a single international patent application, known as PCT Application, effective in partnered countries.

If you are a resident of a PCT Contracting State, you can apply for patents in different nations at the same time. Moreover, you must submit a PCT application in a single language in a receiving office. Additionally, the PCT application will be a corresponding application in India.

International Patenting Applications Stages

1. PCT Application
2. International Search
3. International Preliminary Examination

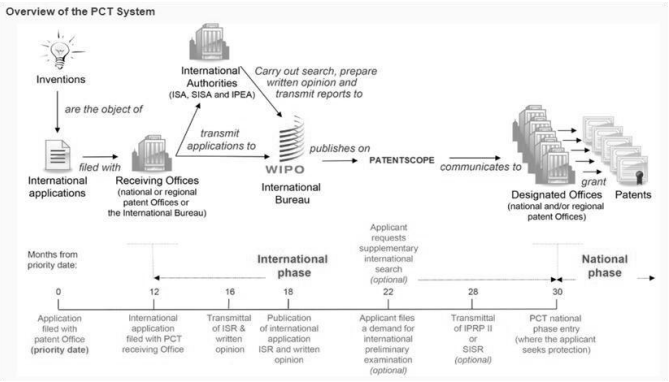
Indian Residents can proceed with international **patent filing** in the following Receiving Office (RO): the Patent Office at Delhi, Chennai, Mumbai, or Kolkata OR the International Bureau of World Intellectual Property Organisation

The Authority to issue patents remains with the national patent Offices that give patents under the law of that country only. Therefore, the applicant has to submit the "national phase" application. Further, in India, the deadline for filing a "national phase" application is 31 months from the first filing date.

International Patent Cost in India

Each stage of the PCT application process involves international patent costs. PCT reduces the significant costs involved in international patent protection by direct applications in each country. However, there are three types of fees included in the PCT process (WIPO PCT Fee Tables as of 27 August 2020) :

1. Transmittal and international filing fees: INR 17,600 (paper filing)
2. A Search Fee for International Search Report (ISR): INR 10,000 (In case of Filing by an individual: INR 2,500)
3. Preliminary examination fees



(a) if the International Search Report (ISR) prepared by the International Searching Authority (ISA): INR 10,000 (in case of Filing by an individual: INR 2,500)

(b) if the International Search Report (ISR) is not prepared by International Searching Authority (ISA): INR 12,000 (in case of Filing by an individual: INR 3,000)

Rights and Responsibilities Of Patentee

A patentee is a person for the time being entered in the register of patents as the grantee or proprietor of a patent. A patentee is the one to whom a patent has been granted. The patentee is entitled to deal with his such property in the same manner as the owner of any other movable property deals with his property**.**

The patentee's rights are enshrined under section 48 of the Patents Act, 1970.

All rights granted to patentee are conditional, which are imposed under section 47 of the Act.

Such conditions are :

1. Manufacture or import of the patented invention may be made by the government for its use.
2. Any process in respect of which the patent is granted may be used by or on behalf of the government for the purpose merely of its use.
3. Any patented process/product may be used for experiment, research, or imparting knowledge to pupils.
4. In case of a patent in respect of any medicine or drug, the medication or drug may be imported by the government for the purpose merely of its own use or for distribution in any dispensary, hospital or other medical institution maintained by or on behalf of the government.

The patentee has been enshrined with the following rights :

- Where the patent is for a product, the exclusive right to prevent third parties, who do not have his consent, from Act of making, using, offering for sale, selling, or importing for those purposes that product in India.

- Where the subject matter of patent is a process, the exclusive right to prevent third parties, who do not have his consent, from the Act of using that process and from the Act of using, offering for sale, selling or importing for those purposes the product obtained directly by that process in India.

The rights conferred under the Act are:

- To exploit the patent.
- To license the patent to another (sec.70).
- To assign the patent to another (sec.70).
- To surrender the patent to another(sec.63).
- To sue for the infringement of the patent

Limitations

The Act provides certain limitations on the exercise of rights. They are:

1) Government use of the patent.
2) Compulsory licenses.
3) Use of inventions for Defence purposes.
4) Revocation for the non-working of patents.
5) Restored patents.

1) Government use of Patent

- Section 100 of the provides that the central government may use the invention for government purposes at any time after the application for a patent has been filed at the patent office or the patent has been granted.
- May be used or even acquired for its use.
- Can do without the patentee's consent or even without paying royalties.
- Includes right to sell.

2) Compulsory Licenses

Section 84 stipulates that at any time after the expiration of three years from the date of grant of patent, any interested person may make an application to the controller for grant of compulsory license on a patent if the patent is not worked satisfactorily to meet the reasonable requirements of the public, at an affordable price.

3) Use of inventions for defense purposes

Such patents may be subject to specific secrecy provisions.

4) Revocation for the nonworking of patents

A patent may be revoked in cases where there has been no work or unsatisfactory result to the public's demand regarding the patented invention.

5) Restored patents

Once lapsed, a patent may be restored, provided that few limitations are imposed on the patentee's right.

Patent Infringement Meaning & Scope

What Is Patent Infringement?

- Patent infringement is the commission of a prohibited act with respect to a patented invention without permission from the patent holder.
- It occurs when someone violates an inventor's patent rights by making, using, or selling the invention without the patent owner’s permission (or if the patent has been licensed), in a way not permitted by the license**.**

Types of Patent Infringement

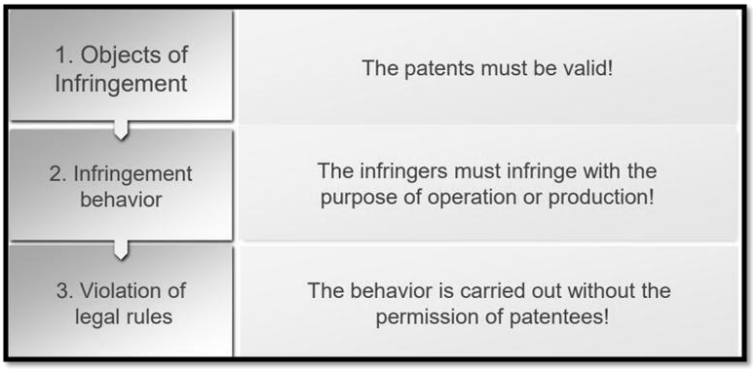
1. Direct Infringement

- It directly states that the third party has willfully or intentionally stolen the technology from the inventor without his prior permission.
- It occurs when someone directly makes, uses or sells the patented invention within the United States.
- Manufacture patented technology
- use patented technology
- offer patented technology for sale;
- sell patented technology
- pass off the patented.

2. Indirect Infringement

- It refers to the unfair practice that does not indicate that the patent is bought and sold in the market.
- It occurs, for instance, when a device is claimed in a patent and a third party supplies a product which can only be reasonably used to make the claimed device
- sell parts that can only be realistically used for a patented invention;
- sell an invention with instructions on using a certain method that infringes on a method patent;
- license an invention that is covered by another's patent;
- sell material components that have been especially made for use in a patented invention and have no other commercial use

Basic Features of Patent Infringement

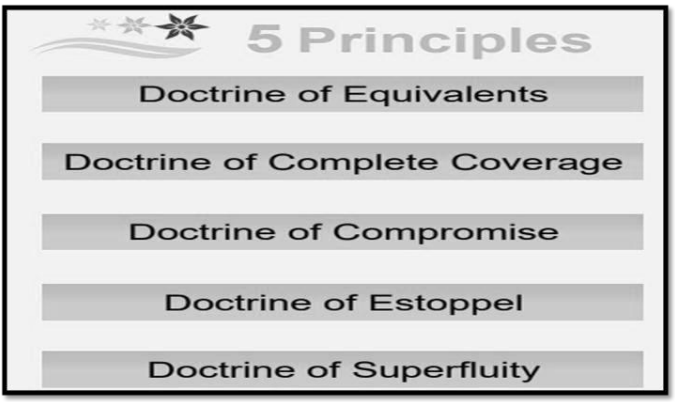


Possible Consequences of Patent Infringement

What consequences can we expect from patent infringement?

1. A huge barrier to independent innovation;
2. Great challenge to the social civilization and sanctity of the law.
3. A damage to the economic laws and laws of value.
4. An illegal behavior that destroys the fair and orderly market competitive order

How to Judge Patent Infringement?

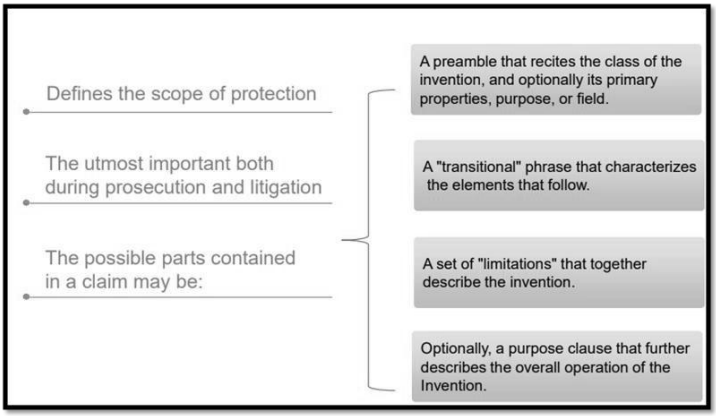


How to Judge Patent Infringement?

A determination of patent infringement involves a two-step process:

1. The claims are analyzed by studying all the relevant patent documents;
2. The claims must "read on" the accused device or process.
3. In a word, the claims are tested to see whether they describe the accused infringement.

About Patent Claims



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Chapter - 8

Artificial Intelligence in Pharmaceutical Sciences

Dr. Narender Boggula
Associate Professor, CMR College of Pharmacy, Kandlakoya,
Medchal, Hyderabad, Telangana, India

Dr. Durgaprasad Kemisetti
Associate Professor, Faculty of Pharmaceutical Science,
Assam Down Town University (ADTU), Gandhinagar, Panikhaiti,
Guwahati, Assam, India

Kanakaraju Vijaya Kishore
Assistant Professor, College of Pharmaceutical sciences, Acharya Nagarjuna University,
Nagarjuna Nagar, Guntur, Andhra Pradesh, India

Sushma Edukulla
Assistant Professor, Bojjam Narasimhulu Pharmacy College for Women,
Vinay Nagar, Saidabad, Hyderabad, Telangana, India

Parijatha Bandigari
Associate Professor, Nalla Narasimha Reddy Education Society's Group of Institutions,
School of Pharmacy, Chowdariguda, Ghatkesar, Medchal, Telangana, India

Abstract

Artificial Intelligence (AI) emerged as an intervention for data and number-related problems. This breakthrough has led to several technological advancements in virtually all fields from engineering to architecture, education, accounting, business, health, and so on. AI has come a long way in healthcare, having played significant roles in data and information storage and management - such as patient medical histories, medicine stocks, sale records, and so on; automated machines; software and computer applications like diagnostic tools such as MRI (Magnetic Resonance Imaging) radiation technology, CT (Computerized Tomography) diagnosis and many more have all been created to aid and simplify healthcare measures. Inarguably, AI has revolutionized healthcare to be more effective and efficient and the pharmacy sector is not left out. During the past few years, a considerable amount of increasing interest in the uses of AI technology has been identified for analyzing as well as interpreting some important fields of pharmacy like drug discovery, dosage form designing, polypharmacology, and hospital pharmacy. Given the growing importance of AI, we wanted to create a comprehensive

report which helps every practicing pharmacist understand the biggest breakthroughs which are assisted by the deployment of this field. This review begins with a brief overview of common AI models, applications in the field of pharmaceutical sciences. Over the last several years, the use of artificial intelligence in the pharma and biomedical industry has gone from science fiction to science fact. Increasingly, pharma and biotech companies are adopting more efficient, automated processes that incorporate data-driven decisions and use predictive analytics tools. The next evolution of this approach to advanced data analytics incorporates artificial intelligence and machine learning. This is concluded that AI is the new evolving field in every sector, even in pharmacy, and it need more development for updating the current scenario as well as for new researches.

Keywords: Artificial intelligence, polypharmacology, drug discovery, drug design, clinical trials.

Introduction

Change matter in every human being's life, like that change is important in various process and various departments, so in field of pharmaceutical sciences and medicine also change is much needed in drug discovery aspects, compounding of chemical products and also manufacturing process of new chemical entities. And artificial intelligence (AI) is the one of the innovative processes which may change the various aspects of pharmaceuticals for the beneficiary purpose of pharmaceutical sciences. There is need of development of novel and innovative principle and interpretation techniques in mechanical and chemical innovation of pharmaceuticals. the use of automated algorithm program which is the most important part of artificial intelligence in pharmaceuticals sciences to carried out various trials is also very beneficial in case of drug discovery.

In the past few decades, the pharmaceutical industry has been limited by the extent of cutting-edge research in pharmaceutical sciences, because the development of new drugs is a long and complex process accompanied by high risks and high costs. In other words, the current field of drug research and development (R&D) requires significant productivity improvements to shorten the cycle time and cost of drug development. Technologies such as network pharmacology, RNA-sequencing (RNA-seq), high-throughput screening (HTS), or virtual screening (VS) have all accelerated the discovery of new targets, as well as new drugs to some extent. Nevertheless, these technologies have rarely been significant contributors to the current process of new drug discovery. Thus, there is an urgent need for new technology to drive the development of new drugs.

The year 2018 has so far been a turbulent time for artificial intelligence (AI). A fatal crash involving a driverless car combined with a scandal where personal data from social media were allegedly repurposed for political and financial gain, and a computer algorithm failing to invite 450,000 English women to breast cancer screening, generating a feeding frenzy for cyber sceptics. Stories of international hacking, whether by foreign governments, criminal gangs, or bored teenagers, have never been far from the printed or web pages of the news outlets. Despite the hype and scaremongering surrounding their coverage, these recent developments highlight the need for serious thinking about the future of both the internet and AI.

AI is a stream of science related to intelligent machine learning, mainly intelligent computer programs, which provides results in a similar way to the human attention process. This process generally comprises obtaining data, developing efficient systems for the uses of obtained data, illustrating definite or approximate conclusions, self-corrections, and adjustments. In general, AI is used for analyzing machine learning to imitate the cognitive tasks of individuals. AI technology is exercised to perform more accurate analyses as well as to attain useful interpretation. In this perspective, various useful statistical models, as well as computational intelligence, are combined in AI technology.

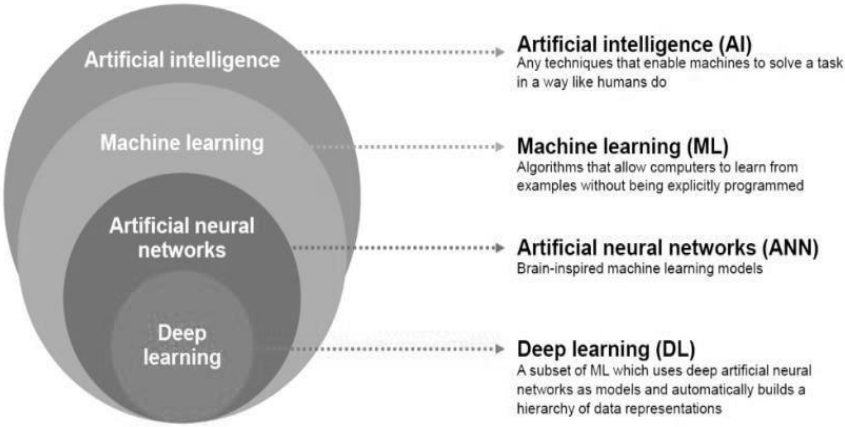

Fig 1: AI intra-relationships

Definition

Artificial Intelligence (AI) refers to the simulation of human intelligence in machines that are programmed to think, learn, and perform tasks typically requiring human intelligence. It is a multidisciplinary field that encompasses

various approaches, including machine learning, natural language processing, computer vision, robotics, and more. AI aims to create systems that can perceive their environment, reason about it, and make decisions to achieve specific goals efficiently. These systems can process large amounts of data, identify patterns, and adapt their behaviour based on new information.

AI has become an integral part of many industries, such as healthcare, finance, transportation, and entertainment. It has the potential to bring about significant advancements and improve various aspects of human life, but it also raises important ethical and societal considerations.

Historical background

In year 1943, the first work which is now recognized as AI was done by Warren McCulloch and Walter pits. They proposed the model of Artificial Neurons. Then the journey of AI has begun. In the year of 1950 Alan Turing developed the Turing Test. In 1952 the term Machine Learning was given. In 1956, The word AI first adopted by American computer scientist John McCarthy at Dartmouth conference. For the first time, AI coined as an academic field. This is known as The Birth of AI. Unimate the first Industrialist Robot joins the assembly line at General Motors and performed automated Die Casting. A few years later in 1964, Eliza was introduced by Joseph Weizenbaum. Using natural language processing, Eliza was able to communicate using pattern matching and substitution methodology to mimic human conversation (superficial communication) serving as the framework for future chatter bots. Then the first AI winter came during the period of 1970s. This fostered the development of The Research Resource on Computers in Biomedicine by Saul Amarel in 1971 at Rutgers University. In 1972 the first humanoid robot created by Japan named WABOT-1. These are the early enthusiasm of AI. The CASNET model is a causal-associational network that consists of three separate programs: model-building, consultation, and a database that was built and maintained by the collaborators. This model could apply information about a specific disease to individual patients and provide physicians with advice on patient management It was developed at Rutgers University and was officially demonstrated at the Academy of Ophthalmology meeting in 1976.

A “backward chaining” AI system, MYCIN, was developed in the early 1970s. Based on patient information input by physicians and a knowledge base of about 600 rules, MYCIN could provide a list of potential bacterial pathogens and then recommend antibiotic treatment options adjusted appropriately for a patient’s body weight. MYCIN became the framework for

the later rule-based system, EMYCIN. Internist-1 was later developed using the same framework as EMYCIN and a larger medical knowledge base to assist the primary care physician in diagnosis. In the year of 1982 AI came back with Expert System. Expert system was programmed that emulate the decision-making ability of human expert. In 1986, DXplain, a decision support system, was released by the University of Massachusetts. This program uses inputted symptoms to generate a differential diagnosis. It also serves as an electronic medical textbook, providing detailed descriptions of diseases and additional references. When first released, DXplain was able to provide information on approximately 500 diseases. Since then, it has expanded to over 2400 diseases.

Table 1: History of artificial intelligence

Year	Achievements
1943	First work known as AI developed
1950	Alan Turing Developed 'Turing Test'
1952	Term 'Machine Learning' given
1956	The word AI first adopted by American computer scientist John McCarthy Known as 'Birth of AI'
1964	Chatbot ELIZA developed
1970	Backward Chaining AI system 'MYSIN' developed
1972	WABOT-1 the first robot created by Japan
1976	CASNET model developed
1982	AI came back with Expert System
1986	DXplain a decision support system developed for information of Diseases
1987-93	Second AI winter began
2011	Robot Pharmacy started using in stores
2012	Technology called DeepQA developed & Google Next launched
2015	Amazon Alexa & Google Assistant launched and Pharmabot a chatbot developed
2016	Companies like Google and Amazon started ML as services
2017	IBM Watson used to successfully identify new RNA-binding proteins
2018	Fast.ai released Deep Learning & Google launched TPU

In the year of 2002 AI first time entered the home in the form of Roomba, a vacuum cleaner and TUG robot were Invented which are used in Hospitals. After the year of 2010 AI grew so much with things like in 2011 IBM's Watson win a quiz and robot pharmacy was introduced in pharmacy stores, in 2012 Google launched Google Now. In contrast to traditional systems that used either forward reasoning (following rules from data to conclusions), backward

reasoning (following rules from conclusions to data), or hand-crafted if-then rules, this technology, called DeepQA, used natural language processing and various searches to analyze data over unstructured content to generate probable answers. This system was more readily available for use, easier to maintain, and more cost-effective. By drawing information from a patient's electronic medical record and other electronic resources, one could apply DeepQA technology to provide evidence-based medicine responses. As such, it opened new possibilities in evidence-based clinical decision-making.

In 2015 many products launched like Amazon Alexa and Google assistant. Also, in 2015 Pharmabot a chatbot developed to assist in medication education for pediatric patients and their parents. In 2016 Companies like Google and Amazon started Machine Learning as Service. In 2017, used IBM Watson to successfully identify new RNA-binding proteins that were altered in amyotrophic lateral sclerosis. In 2018 Fast.ai releases deep learning and Google released TPU (Tensor Processing Unit) and that are how the proliferation of AI continues. In this era AI also entered in the field of Pharmaceuticals and found useful in many places like Drug Discovery & Design, Improvising Industries, Hospital Pharmacy, Pharmacology, Drug Delivery systems etc. Software CAD (Computer aided Drug Design) is so much helpful in the drug design. Also, 3D printing of Drugs is possible through Artificial Intelligence.

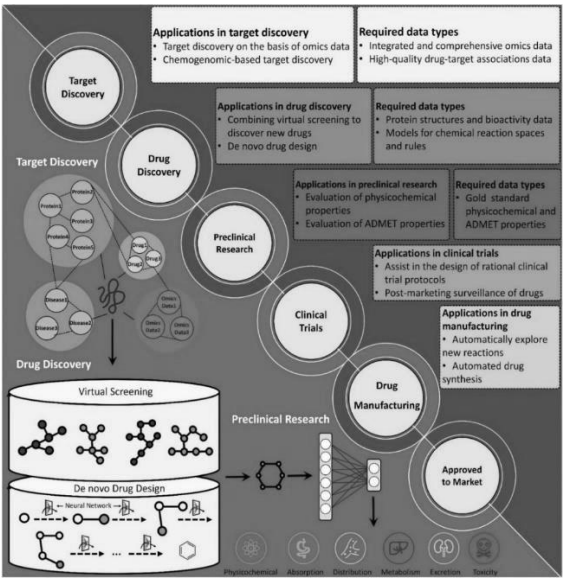

Fig 2: Summary of AI applications in the pharmaceutical sciences (ADMET: absorption, distribution, metabolism, excretion, and toxicity)

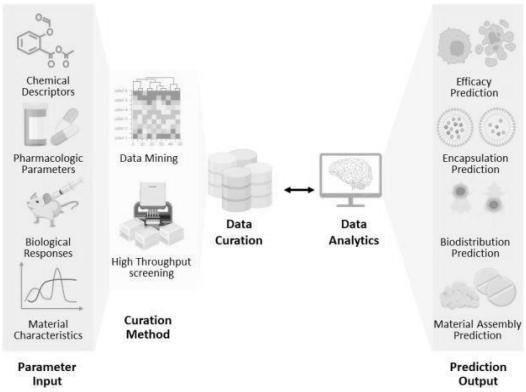

Fig 3: Using a combination of data curation and ML to enhance the development of nanomedicines

Artificial intelligence in drug discovery

The vast chemical space, comprising $>10^{60}$ molecules, fosters the development of a large number of drug molecules. However, the lack of advanced technologies limits the drug development process, making it a time-consuming and expensive task, which can be addressed by using AI. AI can recognize hit and lead compounds, and provide a quicker validation of the drug target and optimization of the drug structure design. Despite its advantages, AI faces some significant data challenges, such as the scale, growth, diversity, and uncertainty of the data. The data sets available for drug development in pharmaceutical companies can involve millions of compounds, and traditional ML tools might not be able to deal with these types of data. Quantitative structure-activity relationship (QSAR)-based computational model can quickly predict large numbers of compounds or simple physicochemical parameters, such as log P or log D. However, these models are some ways from the predictions of complex biological properties, such as the efficacy and adverse effects of compounds. In addition, QSAR-based models also face problems such as small training sets, experimental data error in training sets, and lack of experimental validations. To overcome these challenges, recently developed AI approaches, such as DL and relevant modeling studies, can be implemented for safety and efficacy evaluations of drug molecules based on big data modeling and analysis. In 2012, Merck supported a QSAR ML challenge to observe the advantages of DL in the drug discovery process in the pharmaceutical industry. DL models showed significant predictivity compared with traditional ML approaches for absorption, distribution, metabolism, excretion, and toxicity (ADMET) data sets of drug candidates.

The virtual chemical space is enormous and suggests a geographical map of molecules by illustrating the distributions of molecules and their properties. The idea behind the illustration of chemical space is to collect positional information about molecules within the space to search for bioactive compounds and, thus, virtual screening (VS) helps to select appropriate molecules for further testing. Several chemical spaces are open access, including Pubchem, Chembank, Drugbank, and ChemDB. Numerous in silico methods to virtual screen compounds from virtual chemical spaces along with structure and ligand-based approaches, provide a better profile analysis, faster elimination of nonlead compounds and selection of drug molecules, with reduced expenditure. Drug design algorithms, such as coulomb matrices and molecular fingerprint recognition, consider the physical, chemical, and toxicological profiles to select a lead compound.

Various parameters, such as predictive models, the similarity of molecules, the molecule generation process, and the application of in silico approaches can be used to predict the desired chemical structure of a compound. Another approach applied a multi objective automated replacement algorithm to optimize the potency profile of a cyclin-dependent kinase-2 inhibitor by assessing its shape similarity, biochemical activity, and physicochemical properties. QSAR modeling tools have been utilized for the identification of potential drug candidates and have evolved into AI-based QSAR approaches, such as linear discriminant analysis (LDA), support vector machines (SVMs), random forest (RF) and decision trees, which can be applied to speed up QSAR analysis.

Artificial intelligence for development of drug delivery system

Generally, the designing of drug delivery systems is related to some disadvantages like prediction of the relationship amongst the formulation factors and responses. This is also related to the therapeutic outcomes and the unpredicted occurrences. In the designing of different kinds of intelligent drug releasing systems, the on-demand dose adjustment or the rates of drug releasing, targeted releasing and drug stability are the important factors. Concerning the self-monitoring systems for releasing of drugs, the suitable algorithms are useful for controlling the quantity as well as the period of drug releasing. Therefore, AI approaches are useful for the prediction of the drug dosing efficacy and drug delivery potential of the various drug delivery dosage forms like, solid dispersions, emulsion and microemulsions, tablets, multiparticulates (beads, microparticles and nanoparticles).

Artificial intelligence in pharmaceutical manufacturing

The involvement of AI in manufacturing is like power boost for the pharmaceutical industry. The AI is continuously changing the manufacturing process, as now modern manufacturing systems with AI are trying to give human knowledge to machines with expanding interest of efficiency and better product quality along with reducing the complexities in the manufacturing processes. AI platforms are making the manufacturing process so easy with the advanced tools like CFD, Reynolds Averaged Navier-Stokes solvers technology that use to review the stress level in machine and misusing the automation in the many pharmaceutical process. In the similar way, mathematical simulations are also producing a progressed ways to deal with complex flow problems in manufacturing.

It has been used in the manufacturing of many compounds like sildenafil, diphenhydramine hydrochloride with the maximum yield and purity as similar as convectional method of manufacturing. The working capacities of granulation has increased up to 600L with the aid of AI technologies and correlated neuro-fuzzy logic. They provide prediction with the help of an equation which determines the quantity of fluid to be added and necessary speed for the granulating machine, as well as the diameter of granules.

Artificial intelligence in polypharmacology

Nowadays 'One disease multiple targets' concept governs over the 'one-disease-one-targets' concept for the advanced realization of pathological process in various disorders at their molecular basis. The phenomenon of 'one-disease-multiple-targets' is known as Polypharmacology. Polypharmacology is emerging as the next paradigm of drug discovery. The polypharmacological approaches aim to discover the unknown off targets for the existing drugs (also known as drug repurposing). There are numerous and useful databases, for example, Pubchem, KEGG, ChEMBL, ZINC, STITCH, Ligand Expo, PDB, Drugbank, Super Target, Binding DB which are accessible for the accomplishment of a variety of important and useful information related to the structure of crystals, chemical features, biological properties, molecular pathways, binding affinities, disease concern, drug targets, etc. AI also helps to discover the databases to sketch polypharmacological molecules/agents. AI has bigger potential for vital developments in medicine disorders and has achieved smart performance in AD detection.

Artificial intelligence in clinical trial planning

The new drug discovery clinical trials are done for specific disease or infection with the purpose of building or checking safety and efficacy of a

particular drug and it requires at least 6 to 10 years with a considerable money investment in completion and the chances of success are less there, which leads to huge loss of industry as well as investor. There are many reasons of failure including shortage of technical arrangements as well as unsuitable patient selection. These losses can be minimized with execution of AI in clinical trials which provides a vast digital data for access. The main step in the clinical trials is the appropriate selection of the patients which takes about 33% of total time and the success rate can be ensured by the correct selection of the patients, if this step is taken wrong then leads to 86% or overall failure of trails.

AI can help in choosing the patient data on the basis of patient specific gene-exposome profile examination for the phase II and III of a specific disease clinical trial which will results in the early expectations of drug target in selected patients. There is a problem of patients who give up at the time of clinical trials, this problem makes the selection process more sensitive otherwise it leads to 30% failure of the clinical trials as well as time and money. This failure may be minimized by keeping close eye on the patient nursing and help them to monitor the rules related to clinical trial. A mobile application was established by AI Cure which is responsible for the close monitoring of regular medication consumption in Phase II trials by patients who are suffering from schizophrenia. This application increased the patient loyalty up to 25% towards the clinical trial and ensuring the success of clinical trial.

Artificial intelligence in quality control

The equilibrium of various factors should be maintained in the manufacturing of the product from the crude material. The back-to-back consistency and Quality control tests on the products are required to maintain for the desired product. These methods probably won't be the best methodology for each situation, so that there is a requirement of AI implementation. Gohel *et al*. considered the dissolution rate profile as an indicator of consistency for batch-to-batch operations with the help of artificial neutral network (ANN), that predict an error of <8% in the dissolution rate of various batch to batch operations. AI can be executed for the guidelines of processes manufacturing to accomplish the product. Gams *et al.* used an AI system which is a collaboration of both human efforts and AI where the primary or preliminary information were analyzed from the various batches and the results from them are kept as prove which were additionally converted into guidelines and examined by various operators to lead the manufacturing set in the future. There are many computerized platforms which

are used to ensure the quality of the product. E.g., Electronic Lab Notebook. With use of data mining and various intelligent techniques in the TQM (Total Quality Management), improves the important methodologies during the complex decision, creating new technologies for the advanced quality product.

Artificial intelligence in product management

Market positioning of product is defined as the mode of building a marketing value or recognition of a product in market where it attracts buyer to buy them. It tries to make a vital element in practical strategies in business for encouraging organizations to make their own matchless personality among all products. The same methodology was followed by a company in the marketing of pioneer brand Viagra, and they focused on other aspects associated with the men's erectile dysfunction but not specifically on the treatment. It has become easier for companies to market their products and get a unique marketing value of their company using the AI strategy plus e-commerce sites for advertisement. Companies are using 'Web Crawlers' as one of the innovative AI platforms for getting a marketing value in online market and help to make a vital element in the market. Companies are trying to make their websites better than their competitors and offering reward system for a short time period which affect their market sale and make them popular.

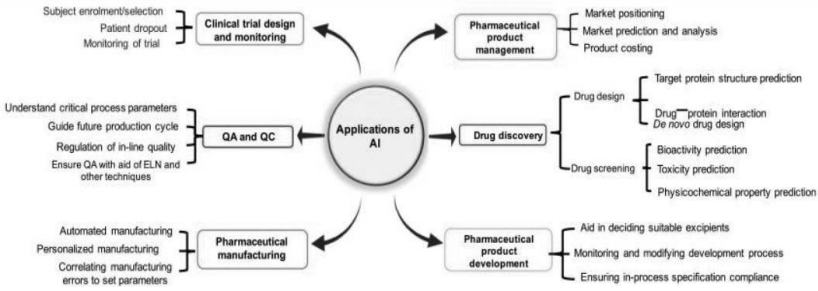

Fig 4: Applications of AI in different subfields of the pharmaceutical industry

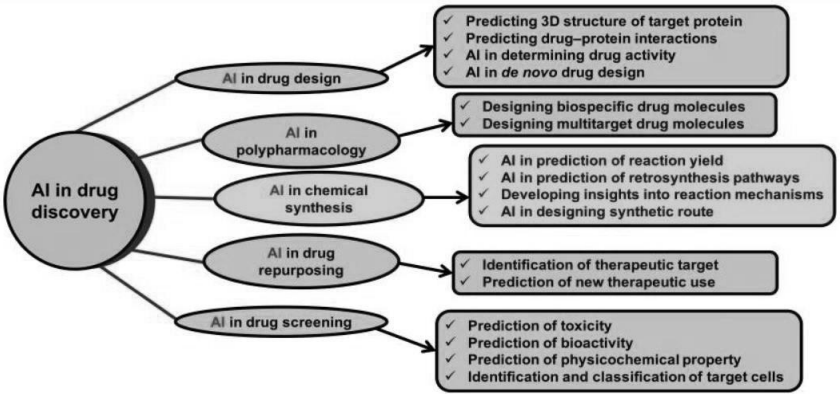

Fig 5: Role of AI in drug discovery

Pharmaceutical market of AI

To decrease the financial cost and chances of failures that accompany VS, pharmaceutical companies are shifting towards AI. There was an increase in the AI market from US$200 million in 2015 to US$700 million in 2018, and is expected to increase to $5 billion by 2024. A 40% projected growth from 2017 to 2024 indicates that AI will likely revolutionize the pharmaceutical and medical sectors. Various pharmaceutical companies have made and are continuing to invest in AI and have collaborated with AI companies to developed essential healthcare tools.

AI in drug interaction and adverse effect prediction

AI in drug interaction and adverse effect prediction involves using machine learning algorithms and computational methods to analyze vast amounts of data related to drugs and patient information. This process helps identify potential drug interactions and adverse effects, thus improving medication safety and patient outcomes. Here's a detailed explanation of how AI is applied in this area:

- **Data Collection:** The first step in drug interaction and adverse effect prediction is gathering relevant data. This includes information from various sources, such as electronic health records (EHRs), clinical trial data, medical literature, drug databases, and patient-reported data. AI systems rely on extensive and diverse datasets to make accurate predictions.
- **Feature Extraction:** Once the data is collected, AI algorithms extract relevant features or attributes from the data. These features may include drug names, dosage, patient demographics, medical

history, genetic information, laboratory results, and other variables that may influence drug interactions or adverse effects.

- **Data Preprocessing:** Before training AI models, the data is pre-processed to handle missing values, standardize data formats, and remove noise or irrelevant information. Data preprocessing is crucial to ensure that the AI algorithms can learn effectively from the data.
- **Training AI Models:** AI models, such as machine learning classifiers or deep learning neural networks, are trained using the pre-processed data. The models learn to recognize patterns and relationships between drugs, patient characteristics, and adverse effects based on the training data.
- **Drug-Drug Interaction Prediction:** AI models can predict potential drug-drug interactions by analyzing drug databases and drug characteristics. The models can identify combinations of drugs that may interact in ways that can lead to adverse effects or reduced efficacy.
- **Drug-Genome Interaction Prediction:** AI can analyze genetic data to understand how individual genetic variations may influence drug responses and metabolism. This allows for personalized medication recommendations, considering an individual's genetic makeup.
- **Adverse Effect Prediction:** AI models use historical patient data and adverse event reports to predict the likelihood of specific adverse effects occurring in certain patient populations. The models take into account various factors, such as drug combinations, dosages, patient demographics, and medical history.
- **Real-Time Decision Support:** AI systems can be integrated into electronic prescribing and pharmacy systems to provide real-time alerts to healthcare providers about potential drug interactions or adverse effects when prescribing medications. This assists pharmacists and physicians in making informed decisions to improve patient safety.
- **Continuous Learning and Improvement:** AI models can continuously learn from new data to improve their accuracy over time. As more data becomes available, the models can refine their predictions and adapt to emerging drug interactions and adverse effects.

The application of AI in drug interaction and adverse effect prediction can help healthcare providers make safer and more effective medication decisions,

reducing the risk of harmful drug combinations and optimizing treatment plans for individual patients. It also contributes to pharmacovigilance efforts by identifying previously unknown adverse effects and potential safety concerns associated with medications.

AI in personalized medicine

AI in Personalized Medicine involves using artificial intelligence techniques to analyze individual patient data, including genetic information, medical history, lifestyle factors, and other relevant data. The goal is to tailor medical treatments and interventions to the specific needs of each patient, considering their unique genetic makeup and characteristics. Here's a detailed explanation of how AI is applied in this area:

- ✓ **Genomic Analysis:** One of the key components of personalized medicine is genomic analysis. AI algorithms can analyze a patient's genetic data to identify genetic variations and mutations that may be associated with certain diseases, drug responses, or treatment outcomes. This information helps in understanding a patient's genetic predisposition to specific conditions and guides personalized treatment decisions.
- ✓ **Drug Response Prediction:** AI models can analyze genomic data to predict how an individual patient will respond to certain medications. By considering genetic factors that influence drug metabolism and effectiveness, AI can recommend the most appropriate medications and dosages for a particular patient, increasing treatment efficacy and reducing adverse reactions.
- ✓ **Disease Risk Assessment:** AI can assess an individual's risk of developing certain diseases based on their genetic profile and other risk factors. This information can be used for preventive measures, early detection, and personalized screening programs.
- ✓ **Treatment Selection and Optimization:** AI can analyze vast amounts of clinical data, medical literature, and treatment outcomes to recommend the most effective treatments for specific conditions and patient profiles. This includes choosing the right drugs, therapies, and interventions tailored to each patient's characteristics.
- ✓ **Clinical Decision Support:** AI systems can integrate with electronic health records (EHRs) and clinical decision support tools to provide real-time recommendations and insights to healthcare providers. This assists clinicians in making well-informed and personalized treatment decisions at the point of care.

- ✓ **Image Analysis:** AI can analyze medical imaging data, such as MRI, CT scans, and X-rays, to identify subtle patterns and markers that may be indicative of specific diseases or treatment responses. This aids in early diagnosis and personalized treatment planning.
- ✓ **Remote Monitoring and Predictive Analytics:** AI-driven wearable devices and health monitoring tools can continuously collect patient data, allowing for real-time monitoring of health parameters. AI algorithms can analyze this data to detect early signs of disease progression or treatment non-compliance, enabling timely interventions.
- ✓ **Drug Development:** AI can be used to optimize drug development by identifying patient subgroups that are more likely to benefit from a new drug. This approach can accelerate clinical trials and increase the chances of successful drug launches.
- ✓ **Patient Education and Engagement:** AI-powered virtual assistants and chatbots can provide personalized health information and support to patients, empowering them to take an active role in managing their health and treatment.

The integration of AI in personalized medicine has the potential to revolutionize healthcare by shifting the focus from a one-size-fits-all approach to targeted and tailored treatments. This not only improves patient outcomes but also reduces healthcare costs by avoiding unnecessary treatments and adverse events. However, it is essential to address privacy and ethical considerations when using sensitive patient data for personalized medicine applications.

Challenges to adoption of artificial intelligence in pharma

The adoption of artificial intelligence in the pharmaceutical industry comes with various challenges. Some of the key challenges include:

- **Data Quality and Availability**: AI algorithms require large, diverse, and high-quality datasets to make accurate predictions. In the pharmaceutical domain, accessing and compiling comprehensive datasets, including clinical trial data, patient records, and drug information, can be challenging due to privacy concerns and data fragmentation across different sources.
- **Data Privacy and Security:** Pharmaceutical data contains sensitive patient information and proprietary research data. Maintaining data privacy and ensuring secure data handling practices are crucial but can be complex and costly, particularly when sharing data between

organizations and collaborating with external partners.

- **Regulatory Compliance:** The pharmaceutical industry is highly regulated, and adopting AI technologies requires compliance with strict regulatory standards. Ensuring that AI algorithms meet regulatory requirements, such as those from the Food and Drug Administration (FDA) and other regulatory bodies, can be a significant barrier to adoption.
- **Interpretability and Explainability:** AI models often work as "black boxes," making it challenging to understand the rationale behind their decisions. In critical medical applications, such as drug discovery or personalized medicine, the lack of interpretability can raise concerns about trust, safety, and ethical implications.
- **Validation and Clinical Adoption:** Validating AI models in clinical settings and gaining acceptance from healthcare professionals is a time-consuming and resource-intensive process. Demonstrating the efficacy and safety of AI-driven interventions is essential for their widespread adoption.
- **Integration with Existing Systems:** Integrating AI technologies into existing pharmaceutical systems and workflows can be complex. Ensuring seamless interoperability and compatibility with Electronic Health Records (EHRs) and other IT infrastructure is necessary for successful implementation.
- **Cost and Return on Investment (ROI**): Developing and deploying AI solutions in the pharmaceutical sector can involve substantial costs, including infrastructure, data storage, and skilled personnel. Demonstrating a clear and tangible return on investment can be a challenge, especially in the early stages of adoption.
- **Talent and Expertise Gap:** There is a shortage of AI experts with domain knowledge in the pharmaceutical industry. Attracting and retaining skilled professionals who understand both AI techniques and the complexities of pharmaceutical research and development can be a significant hurdle.
- **Resistance to Change:** Introducing AI-driven processes and decision-making systems might face resistance from stakeholders who are not familiar with AI technologies or fear potential job displacement.
- **Ethical Concerns:** AI applications in pharma raise ethical considerations related to data privacy, consent, transparency, and the

potential biases in AI algorithms. Ensuring ethical AI development and deployment is essential to gain trust from patients, healthcare professionals, and regulatory bodies.

Despite these challenges, the potential benefits of AI in the pharmaceutical industry are substantial, and ongoing efforts are being made to address these issues. Collaborations between researchers, industry players, and regulatory bodies can help overcome obstacles and drive responsible and meaningful AI adoption in the pharma sector.

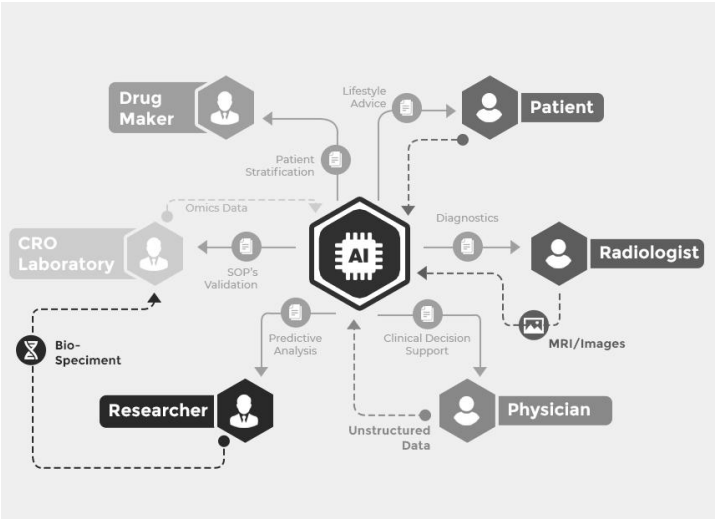

Fig 6: AI in the pharmaceutical industry

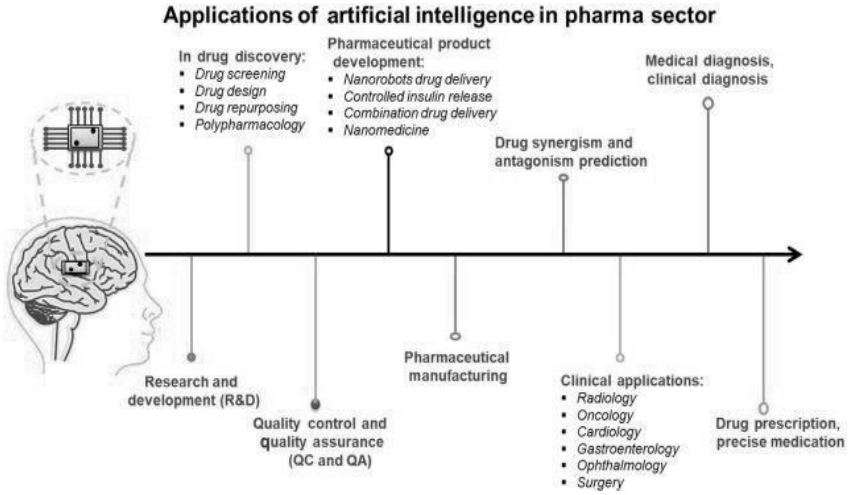

Fig 7: Applications AI in pharma sector

AI based advanced applications

AI-based nanorobots for drug delivery:

Nanorobots comprise mainly integrated circuits, sensors, power supply, and secure backup of data, which are maintained via computational technologies, such as AI. They are programmed to avoid the collision, target identification, detect and attach, and finally excretion from the body. Advances in nano/microrobots give them the ability to navigate to the targeted site based on physiological conditions, such as pH, thus improving the efficacy and reducing systemic adverse effects. Development of implantable nanorobots developed for controlled delivery of drugs and genes requires consideration of parameters such as dose adjustment, sustained release, and control release, and the release of the drugs requires automation controlled by AI tools, such as NNs, fuzzy logic, and integrators. Microchip implants are used for programmed release as well as to detect the location of the implant in the body.

AI in combination drug delivery and synergism/antagonism prediction:

Several combinations of drugs are approved and marketed to treat complex diseases, such as TB and cancer, because they can provide a synergistic effect for quick recovery. The selection of precise and potential drugs for combination requires high-throughput screening of a considerable number of drugs, making the process tedious; for example, cancer therapy requires six or seven drugs as a combination therapy.

AI emergence in nanomedicine:

Nanomedicines use nanotechnology and medicines for the diagnosis, treatment, and monitoring of complex diseases, such as HIV, cancer, malaria, asthma, and various inflammatory diseases. In recent years, nanoparticle-modified drug delivery has become important in the field of therapeutics and diagnostics because they have enhanced efficacy and treatment. A combination of nanotechnology and AI could provide solutions to many problems in formulation development.

Conclusion

In the short term, we can expect to see even more small biotech and software companies exploring ways of leveraging AI to address particular niches in the drug discovery and development pipeline. While many will either fail or run out of money, others are likely to succeed well enough to become sustainable, and probably to be acquired by bigger players. If AI does indeed help to discover drugs, as we expect that it will, in the medium term it will be increasingly integrated into the working practices of organisations both large

and small. It will also change the way we do academic science, with patterns within and connections between data being discovered automatically in large quantities. It is certainly necessary to think about effects on employment; many jobs will change, some undoubtedly disappear, and in all likelihood new kinds of role for researchers and managers interfacing with AI will be created. Recent technological advances, from the Human Genome Project to high throughput screening, have been sold on their ability to discover more, better, and often more personalised medicines. AI will be no exception is this regard, and indeed it offers the prospect of leveraging the other advances of the last 20 years or so to improve the productivity of the industry and better meet patients' needs. Nevertheless, there are justifiable fears about potential data misuse, about the balance between AI and human control, and about the impact on employment and on employees' roles in the organisation.

AI is at the center of a new enterprise to build computational models of intelligence. The main assumption is that intelligence (human or otherwise) can be represented in the terms of symbol structures and symbolic operations which can be programmed in a digital computer. There is much debates as to whether such an appropriately programmed computer would be a mind, or would merely simulate one, but AI researchers need not wait for the conclusion to that debate, nor for the hypothetical computer that could model all of human intelligence. Aspects of human intelligent behaviour, such as solving problems, making references, learning, and understanding language, have already been coded as computer programs, within very limited domains, such as identifying diseases of soybean plants, AI programs can outperform human experts. Now the great challenge of AI is to find ways of representing the commonsense knowledge and experience that enables people to carry out every day activities such as holding a wide-ranging conversation, or finding their way along a busy street.

The human body is the most advanced machine that has ever been built. The human brain is actively attempting to develop something that is significantly more effective than a human being at performing any given task, and it has had remarkable success in doing so to some level. The field has undergone a significant transformation thanks to AI tools such as the robotic pharmacy, pull robot, and Watson for cancer. The infrastructure required for the health-care industry will need to be more sophisticated and technologically advanced as it grows. The creation and use of algorithms for data analysis, learning, and interpretation constitute AI. The AI technology is very useful in pharmaceuticals, as the uses of AI technology has been analysing and interpreting some fields of pharmacy like dosage form designing,

polypharmacology, drug discovery, hospital pharmacy etc. Artificial Intelligence provide accurate information on patients and expected outcomes with successful result obtained by worldwide data.

AI can also make major contributions to the further incorporation of the developed drug in its correct dosage form as well as its optimization, in addition to aiding quick decision-making, leading to faster manufacturing of better-quality products along with assurance of batch-to-batch consistency. AI can also contribute to establishing the safety and efficacy of the product in clinical trials, as well as ensuring proper positioning and costing in the market through comprehensive market analysis and prediction. Although there are no drugs currently on the market developed with AI-based approaches and specific challenges remain with regards to the implementation of this technology, it is likely that AI will become an invaluable tool in the pharmaceutical industry in the near future. Now the great challenge of AI is to find ways of representing the commonsense knowledge and experience that enables people to carry out every day activities such as holding a wide-ranging conversation, or finding their way along a busy street.

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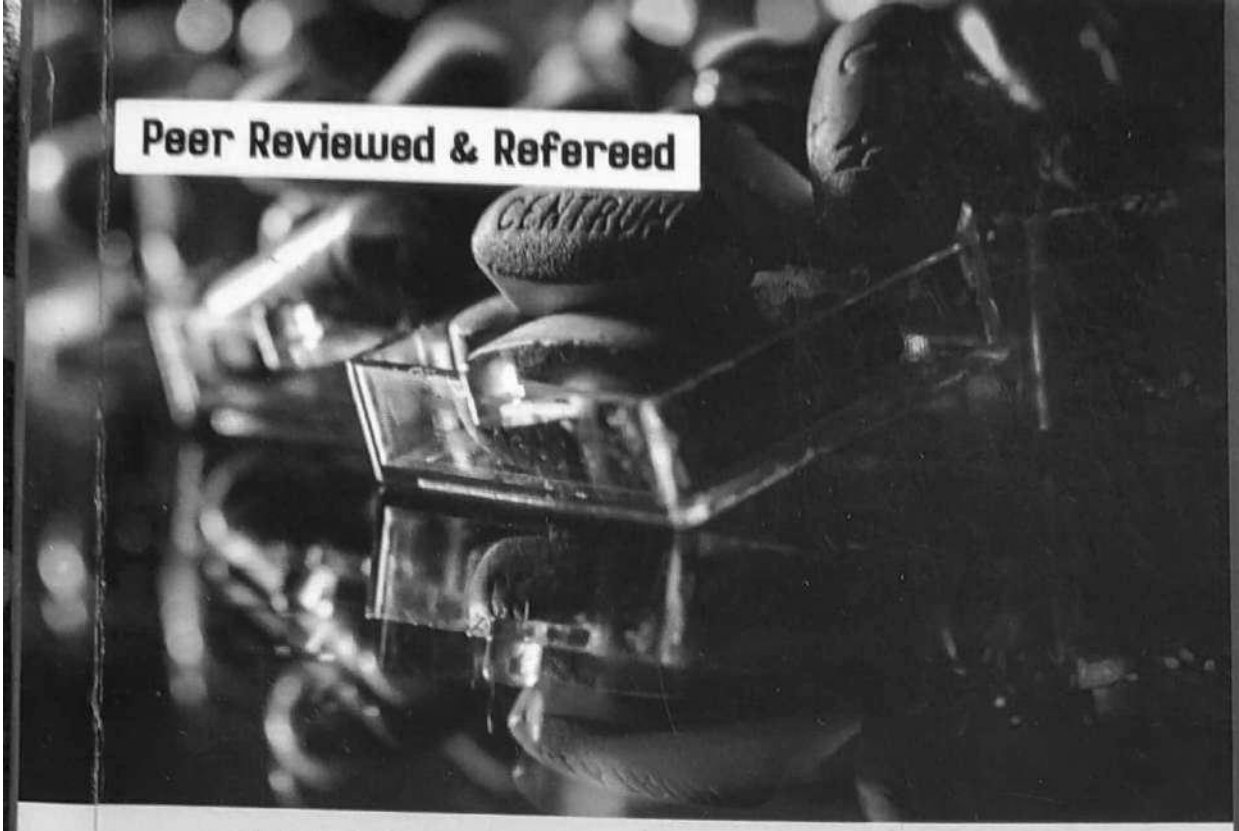

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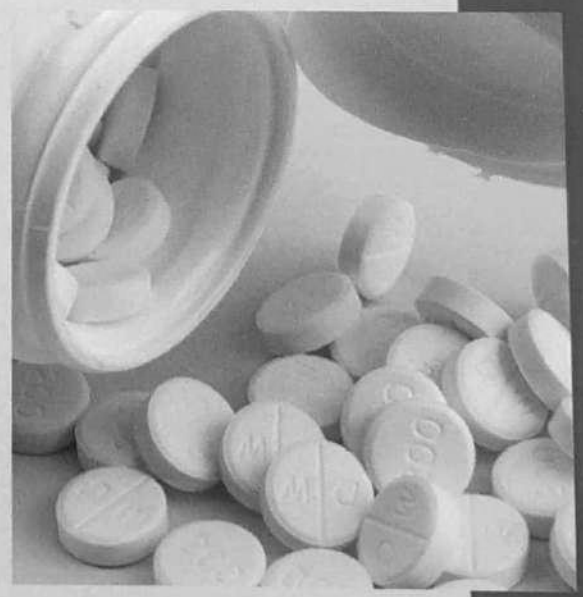

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Chapter - 7
A Literature Based Review on Liquid Chromatography-Mass Spectrometry (LC-MS)

Authors

Prashanthi Kamatam

Assistant Professor, Nalla Narasimha Reddy Education Society's Group of Institutions, School of Pharmacy, Chowdariguda, Ghatkesar, Telangana, India

Prapulla Putta

Assistant Professor, Mother Teresa College of Pharmacy, NFC Nagar, Ghatkesar, Hyderabad, Telangana, India

Sahithi Alapati

Assistant Professor, Nalla Narasimha Reddy Education Society's Group of Institutions, School of Pharmacy, Chowdariguda, Ghatkesar, Telangana, India

Chaitanya Aavula

Assistant Professor, Nalla Narasimha Reddy Education Society's Group of Institutions, School of Pharmacy, Chowdariguda, Ghatkesar, Telangana, India

Chapter - 7

A Literature Based Review on Liquid Chromatography-Mass Spectrometry (LC-MS)

Prashanthi Kamatam, Prapulla Putta, Sahithi Alapati and Chaitanya Aavula

Abstract

Chromatography is a non-destructive procedure for separating a mixture of components in to individual components with the help of a porous medium under the influence of solvents. Before 2004, High Performance Liquid Chromatography (HPLC) was the most frequently used technique for separating a mixture of components into individual components. But due to some limitations, a new technique has been introduced by the scientist which is highly efficient and advanced and also overcome some of the limitation of HPLC and the technique popularly known as Ultra Performance Liquid Chromatography (UPLC). UPLC can be regarded as latest invention for liquid chromatography. It brings drastic changes in sensitivity and speed of analysis. It has instrumentation that can be operated at higher pressure as compared to HPLC. In the last decade, the tremendous improvement in the sensitivity and also affordability of liquid chromatography-tandem mass spectrometry (LC-MS/MS) has revolutionized its application in pharmaceutical analysis, resulting in widespread employment of LC-MS/MS in determining pharmaceutical compounds, including anti-cancer drugs in pharmaceutical research and also industries. The Liquid Chromatography-Mass Spectrometry (LC-MS) is a powerful analytical technique with very high sensitivity and specificity. LC-MS is combination of Liquid Chromatography (LC) and Mass Spectrometry (MS). With the Liquid Chromatography (LC) the separation of components can be done and then the sample eluents from LC are transferred into Mass Spectrometry (MS) where the detection, identification and determination of masses of components can be done in presence of other components. LC-MS is used in determination, of pharmaceutical drug substances, intermediates and its related compounds for quantitative and qualitative purpose. LC-MS is used most significantly in *in-vitro* dissolution, bio-equivalence, bioavailability and metabolite studies.

Keywords: Liquid Chromatography-Mass Spectrometry (LC-MS), quantification, validation, High Performance Liquid Chromatography (HPLC), Ultra Performance Liquid Chromatography (UPLC)

Introduction

Importance of drug analysis

'Health is wealth'. It is vital fact that a healthy body is desire of every human being. Good health is first condition to enjoy the life and all other things which mankind is having. Nowadays peoples are more concentrating towards health. Even governmental bodies of different countries and World Health Organization (WHO) are also focusing for health of human being. Health care is prevention, treatment and management of illness and preservation of mental and physical well-being. Health care embraces all the goods and services designed to promote health including preventive, curative and palliative in interventions. The health care industry is considered an industry or profession which includes people's exercise of skill or judgment or providing of a service related to the prevention or improvement of the health of the individuals or the treatment or care of individuals who are injured, sick, disabled or infirm. The delivery of modern health care depends on an interdisciplinary Team.

The medical model of health focuses on the eradication of illness through diagnosis and effective treatment. A traditional view is that improvement in health results from advancements in medical science. Advancements in medical science bring varieties of medicines. Medicines are key part of the health care system. The numerous medicines are introducing into the world-market and also, that is increasing every year. These medicines are being either new entities or partial structural modification of the existing one. So, to evaluate quality and efficacy of these medicines is also important factor. Right from the beginning of discovery of any medicine quality and efficacy of the same are checked by quantification means. Quality and efficacy are checked by either observing effect of drug on various animal models or analytical means. The option of animal models is not practically suitable for every batch of medicine as it's required long time, high cost and more man-power. Later option of analytical way is more suitable, highly precise, safe and selective.

The analytical way deals with quality standards which are assigned for products to have desirable efficacy of the medicines. Sample representing any batch are analyzed for these standards and it is assumed that drug/medicine which is having such standards are having desire effect on use. Quality control is a concept, which strives to produce a perfect product by series of measures

designed to prevent and eliminate errors at different stage of production. The decision to release or reject a product is based on one or more type of control action.

Due to rapid growth of pharmaceutical industry during last several years, number of pharmaceutical formulations are entered as a part of health care system and thus, there has been rapid progress in the field of pharmaceutical analysis. Developing analytical method for newly introduced pharmaceutical formulation is a matter of most importance because drug or drug combination may not be official in any pharmacopoeias and thus, no analytical method for quantification is available. To check the quality standards of the medicine various analytical methods are used. Modern analytical techniques are playing key role in assessing chemical quality standards of medicine. Thus, analytical techniques are required for fixing standards of medicines and its regular checking. Out of all analytical techniques, the technique which is widely used to check the quality of drug is known as 'CHROMATOGRAPHY'.

Liquid Chromatography-Mass Spectrometry (LC-MS) is quickly becoming the preferred tool of liquid chromatographers. It is a powerful analytical technique that agglutinate the resolving powerful of liquid chromatography with the detection specificities of mass spectrometry. Liquid Chromatography-Mass Spectrometry (LC-MS) is now becoming routine technique with the advancement of electrospray ionisation (ESI) provide a simple and robust interface. Since the newly developed API-based methods produce mild ionization, for structural elucidation studies it can be complemented by invoking fragmentation-induced collisions in the interface itself or by recourse to LC-Tandem MS as realized with the help of a triple quadrupole system. It is applicable for of biological molecules and the use of tandem MS and stable isotope internal standards allows highly sensitive and accurate methods to be enlarge through some method optimisation to minimise ion repression effects. Method validation is of important between the process of drug discovery and development.

The LC-MS data may be used to provide information about the molecular weight, structure, identity and quantity of particular sample components. The study determines of the selectivity, specificity, LOD, LOQ, linearity, range, accuracy, precision, recovery, stability, ruggedness, and robustness of liquid chromatographic studies.

LC-MS today holds enormous potentials for improvements in the pharmaceutical fields and laboratory medicine mainly including therapeutic drug monitoring, endocrinology, toxicology and metabolic analyses,

therefore, hyphenated techniques are examples of new tools that adopted for developing fast and cost-effective analytical methods. One of the most prevalent hyphenated techniques, LC-MS, has led to major breakthroughs in the field of quantitative bioanalysis since the 1990s due to its inherent specificity, sensitivity, and speed. It is now generally accepted as the preferred technology for quantitating small molecule drugs, metabolites, and other xenobiotic biomolecules in biological matrices as like plasma, blood, serum, urine, and tissue. Estimation of drugs and their metabolites in biological matrix is very tricky compared to in formulations. Biological matrix (e.g., blood, plasma, serum and urine) samples contain mostly water and other biological components like dissolved proteins, glucose, clotting factors, mineral ions, hormones and acids etc.

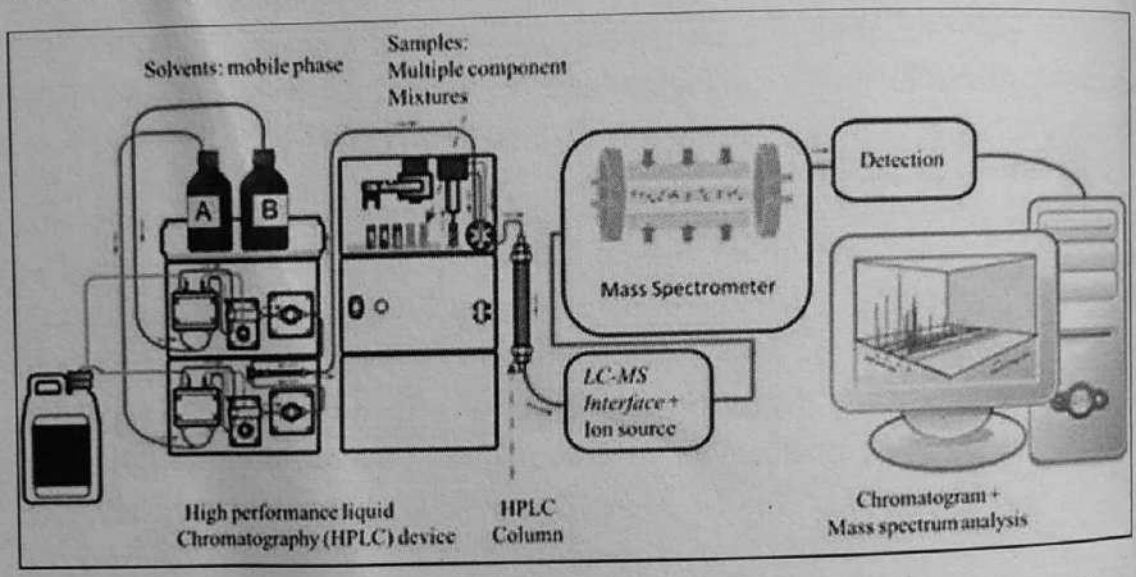

Fig 1: Direct electron ionisation Liquid Chromatography-Mass Spectroscopy

Principle

In principle, the mixture of components to be separated is loaded on an autosampler, injected into an LC stream of mobile phase and separated on a column. The eluting fractions are then detected by a mass analyser (or commonly an in-line UV/DAD detector followed by a mass analyser) via ionisation in one of a number of techniques (EI, ESI, APCI, APPI, ESCI etc.). With respect to the LC setup, this can be HPLC or UPLC depending on the analytical method and there are obvious merits for each. There are a multitude of options on the characteristics of the mass analyser.

LC

Chromatography separates the mixture using the differences of the distribution coefficient between the two phases (mobile and stationary phase). According to the state of the mobile phase, chromatography can be divided into gas chromatography, liquid chromatography, and supercritical fluid

chromatography, while, according to the geometric forms of the stationary phase, chromatography can be divided into column chromatography, paper chromatography, and thin layer chromatography. The most commonly used LC method is column chromatography which regards liquid as a mobile phase. High performance liquid chromatography (HPLC) is modified based on the classic liquid column chromatography.

The application of LC is divided into two categories. One of them is qualitative or quantitative for a particular composition. Qualitation is managed according to the consistency between the sample and the target component in the peak time. Quantitation is performed according to the standard curve generated after standards are injected at different concentration levels. The other one is a fingerprint which refers to the notion that, after the fingerprint sample has been disposed of in some way, we can obtain chromatogram or spectrogram labelled chemical characteristics by using certain methods of analysis. LC has a great advantage on the capability of separating complex samples, so it is the most effective option when applied to separate mixtures, but not suitable to obtain structural information of the material. Qualitation finished by the contrast between the peak positions of unknown compounds and the standards is not available for monitoring of unknown compounds.

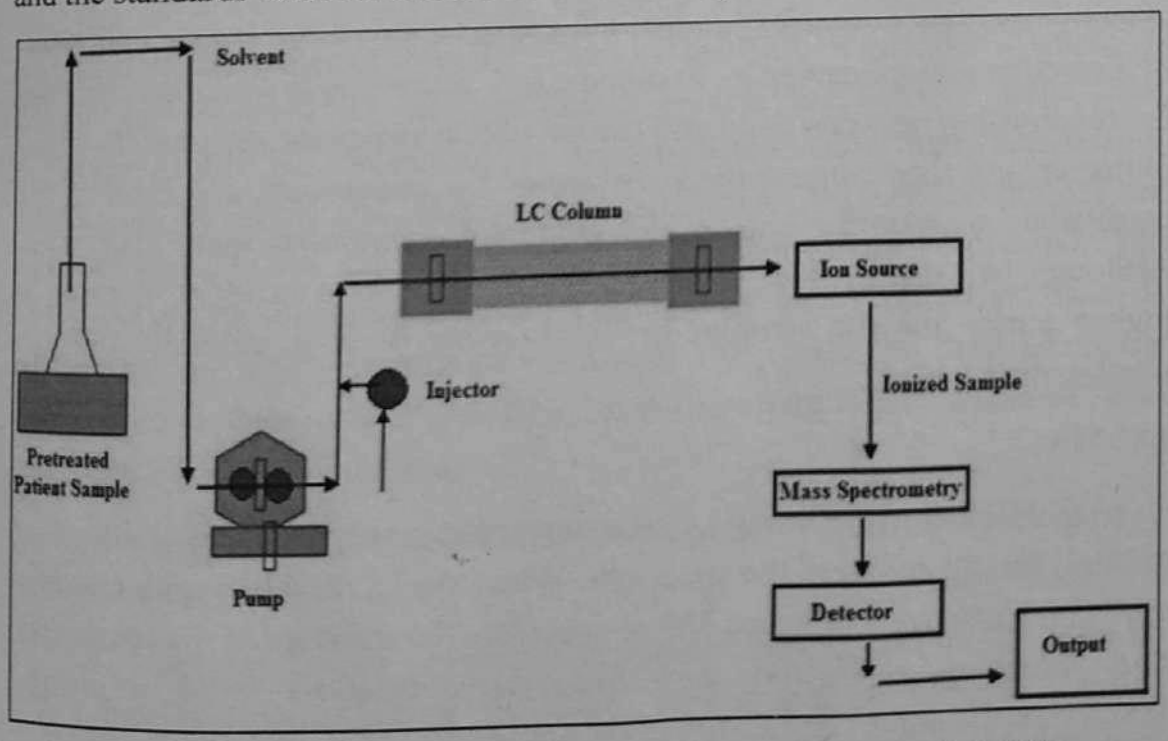

Fig 2: Principle-Liquid Chromatography-Mass Spectroscopy (LC-MS)

MS

Mass spectrometry is widely used in the field of TCM research due to its high selectivity, high sensitivity, and capability of providing information including relative molecular mass and structural characteristics. MS

completes the qualitation using molecular mass and relevant structural information and completes quantitation by the relationships of the peak and compound content which the peak represented. Atmospheric Pressure Ionization (API) of MS has Electro Spray Ionization (ESI) and Atmospheric Pressure Chemical Ionization (APCI). For many types of compounds, ESI has high sensitivity. Compared with ESI, APCI is suitable for the less polar compounds and the analysis of volatile compounds. Depending on the differences among mass analyzers used, common MS concludes Quadrupole Mass Spectrum (Q-MS), Time-Of-Flight Mass Spectrum (TOF-MS), and Ion Trap Mass Spectrometry (IT-MS).

Tandem mass spectrometry refers to two or more MS working together. The most commonly used tandem mass spectrometry is triple-Quadrupole Mass Spectrometry (QQQ-MS). In order to use quadrupole to conduct multistage mass spectrometry, three quadrupoles are sequentially placed, which is triple quadrupole. Another type of tandem mass spectrometry, such as Quadrupole-Time-Of-Flight Mass Spectrometry (Q-TOF-MS) and Quadrupole-Ion Trap Tandem Mass Spectrometry (Q-IT-MS) also consists of a variety of quality analyzer series. Ion trap time series can achieve multistage MS scans sequentially at different times, so this study categorized IT-MS as tandem mass spectrometer. Tandem mass spectrometry can induce fragments of molecular ions generated by first-stage MS, according to which we can infer the relationship between child and parent, obtain structural information of the molecule and then suggest the structure of the compound, and conduct the qualitation analysis for known and unknown compounds more accurately. Although MS can provide structural information of a material, it requires higher purity for the sample. In TCM research, it is generally used in combination with LC.

LC-MS

LC-MS technique, using LC as a separation system and MS as a detection system, finally achieves the spectrum. When the LC and MS work together, they can carry out multistage MS to speculate the structure of the compound, thus finishing qualitative and quantitative analysis more accurately. Retrieving the papers on LC-MS in the application of TCM research literatures published during the past five years at home and abroad, we found that they could be separated into two categories, that is, LC-Q-MS and LC-MS/MS. In order to analyze the differences and the advantages and disadvantages of each method, papers were classified according to the difference of tandem mass spectrometry.

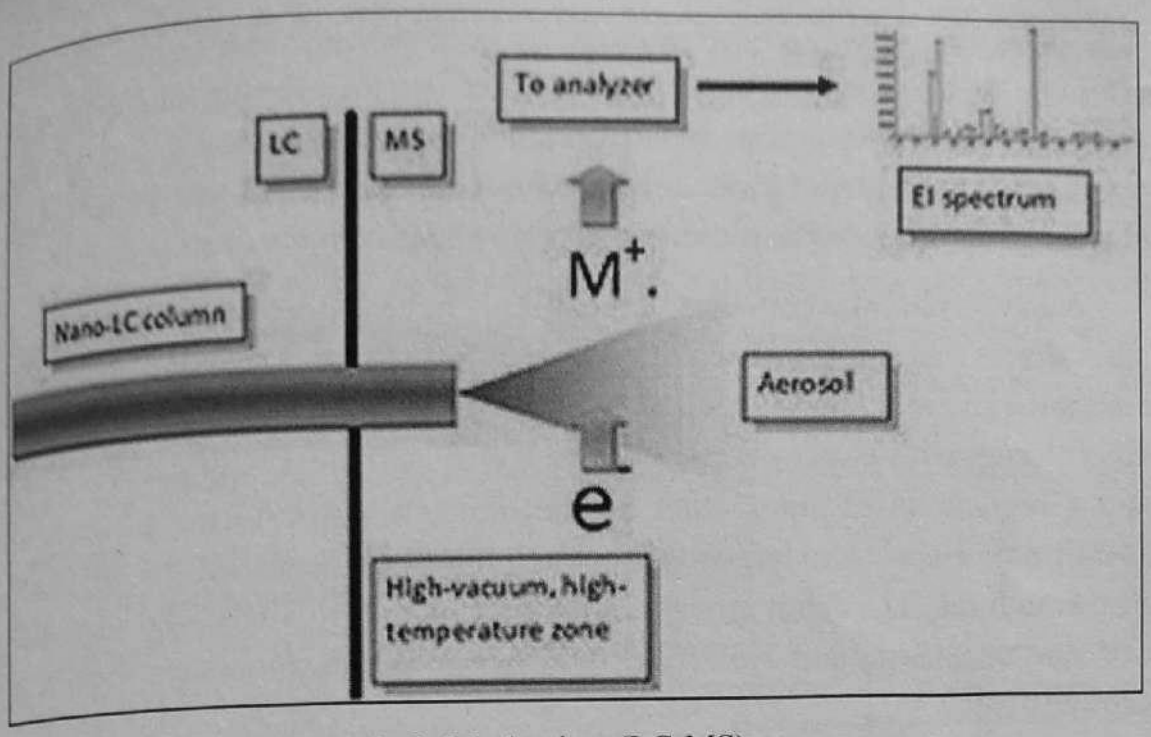

Fig 3: Mechanism (LC-MS)

Drug discovery & development

The goal of the drug discovery stage is to generate a novel lead candidate with suitable pharmaceutical properties (i.e., efficacy, bioavailability, toxicity) for preclinical evaluation. Potential lead compounds contained in natural product sources or from the extensive database of a synthetic amalgam library are screened for activity. Lead compounds identify field from screening efforts are optimized in closed collaboration with exploratory metabolism programs and drug safety evaluations. 100,000 compounds are typically required for the discovery a single quality lead compound. The process of identifying a lead compound can take up to 2-4 years. Optimization of the resulting lead may take an additional 1-2 years. The drug discovery stage involves three primary analysis activities: target identification; lead identification; and lead optimization.

LC-MS applications and advances for discovery chemistry accessing compound identity and purity

The medicinal chemist's objective is to develop drug-like molecules with high affinity/activity to test in the clinic. This is met by building a broad understanding of the structure-activity and structure-property relationships (SAR, SPR) through an iterative process of molecular design, synthesis and hypothesis testing (activity or molecular properties). The goal of the analytical scientist is to implement LC-MS systems that yield maximum capability for laboratories challenged by throughput requirements. LC-MS open access service (analysis carried out by chemists with minimum training on sample

submission) has become the standard technique to monitor the progress of synthetic reactions in real time and/or verify the identity and purity of compounds from structure–activity relationship (SAR) studies. Maximizing purification through put purification of compounds typically takes a medicinal chemist from 25 to 50% of their laboratory time.

Many pharmaceutical companies have developed purification laboratories to build a technology platform that integrates processes, technologies, methodologies and data management. Centralized purification laboratories with experimental knowledge in analytical/medicinal chemistry and a high level of automation are becoming a powerful line of attack to sustain small-scale and large-scale achiral/chiral purification at different levels of throughput. The leading technology involved in this scenario is LC with UV and/or MS-guided collection, which can deliver thousands of purified samples/week.

Drug discovery environment

In order to be useful, information from pharmaceutical profiling must match the needs and preferences of discovery scientists. Drug discovery research is an increasingly complicated and challenging field. Tried and true strategies are always the primary focus and new strategies must prove themselves in order to be accepted. Four elements of discovery research that are critical to consider in developing a pharmaceutical profiling program are:

Primary focus on high affinity ligands. The need for information to guide decisions. The need for speed. Diversity and numbers. The use of high-performance liquid chromatography joined with mass spectrometry (HPLC-MS) or tandem mass spectrometry (HPLC-MS-MS) has proven to be the analytical technique of choice for most assays used in various stages of new drug discovery. New drug discovery can be defined as the process whereby compound libraries are screened, then hits are selected and modified to become leads that are optimized until a compound emerges that can be developed into a drug candidate. HPLC-MS and HPLC-MS-MS are used for the analysis of newly synthesized compounds that become part of a compound library. These assays check that the correct compound has been synthesized and that the purity is sufficient to be used in the library.

In a second stage, various physical and chemical properties (e.g. physiological solubility, permeability and chemical stability) of these new chemical entities (NCEs) are assessed and HPLC–MS is often used for these assays. Furthermore, there are also a series of drug metabolism and pharmacokinetics (DMPK) tests that are performed as part of new drug

discovery; these tests measure the absorption, distribution, metabolism and excretion (ADME) properties of the NCE, as well as the pharmacokinetic (PK) parameters of the molecule. Most of these assays rely on HPLC-MS or HPLC-MS-MS for the measurement step. This review will provide an overview of the various ways in which LC-MS (which will be used as a term that includes both HPLC-MS and HPLC-MS-MS) can be used in the new drug discovery process. The review will also provide an introduction into the various types of mass spectrometers that can be selected for the multiple tasks that can be performed using LC-MS as the analytical.

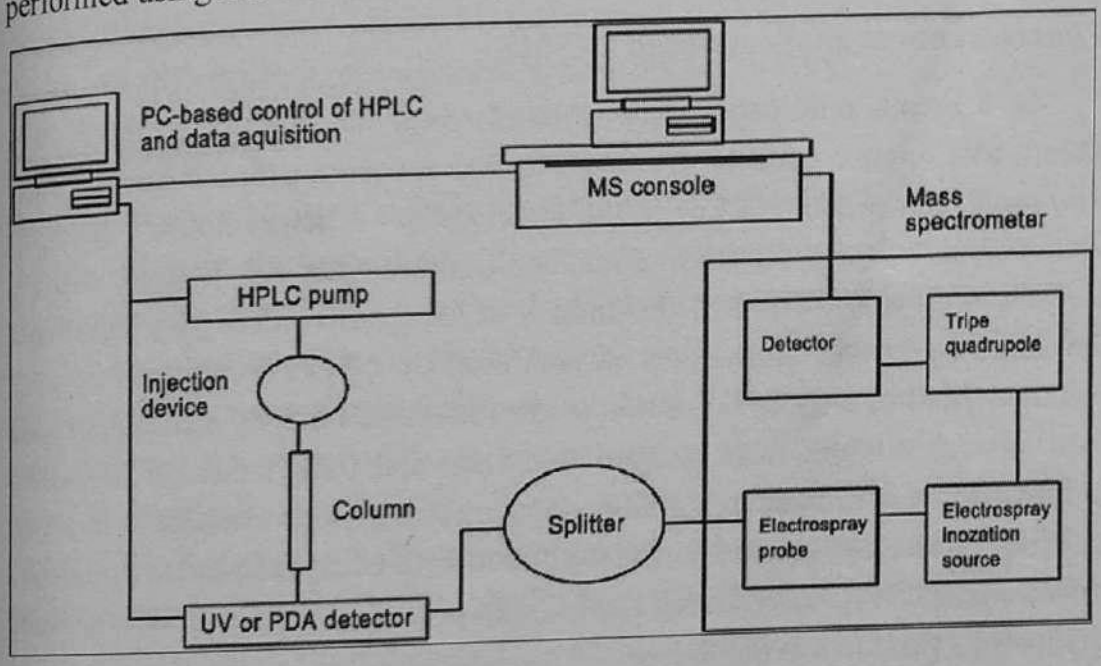

Fig 4: Instrumentation diagram

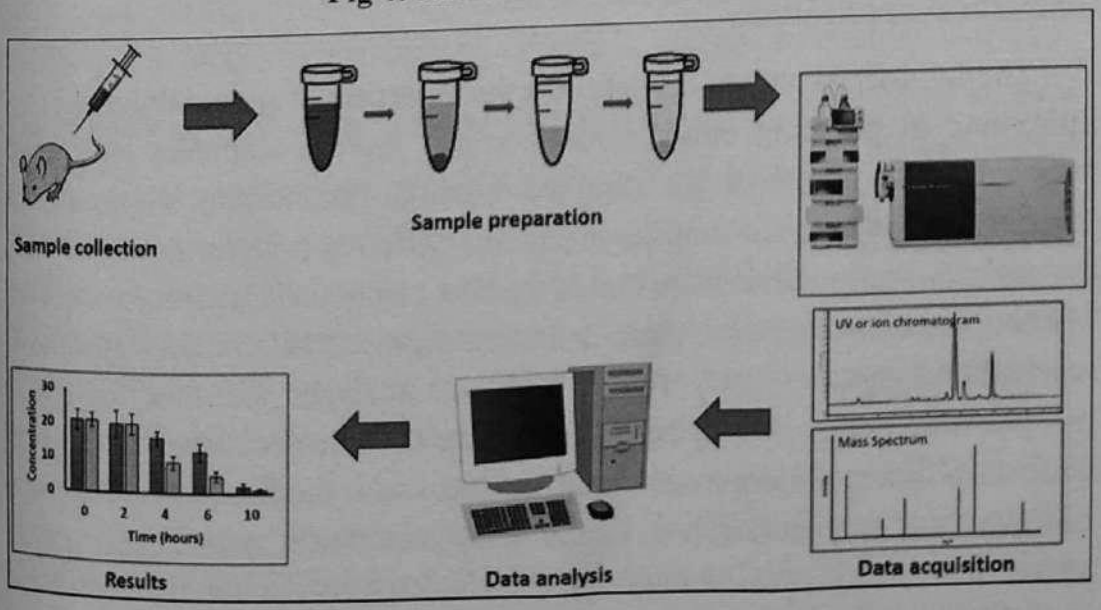

Fig 5: LC-MS services for standard and custom methods

The use of LC-MS in pharmaceutical process development

The use of LCMS in a pharmaceutical setting is well established as analysts have always sought the best quality information from detectors and

the outlay involved in set-up has significantly decreased. The seeding point for much of what is described below has been in the industrial QA/QC laboratories (due to the obvious qualitative and quantitative data produced) but also in academic collaborations. Recently, the application of LC-MS (in tandem with other qualitative and theoretical techniques) to process development has gained significant momentum. Outlined below are some recent developments in the use of LC-MS applied to process development change, a very significant area in pharmaceutical chemistry having achieved global investment in the past decade.

Pharmaceutical applications of LC-MS

In a recent publication from AstraZeneca, the process synthesis of a potent SRC kinase inhibitor (AZD0530) was revealed with the use of LCMS and molecular modelling key to the development. The preliminary synthetic route involved three successive nucleophilic aromatic substitutions and the key focus of this work was the final SnAr reaction which gave significant levels of by-product formation as identified by HPLC (and relatively poor isolated yield of only 63%). Initial studies identified that by a change of base and solvent mixture from sodium t-amylate and t-amyl alcohol to sodium hydroxide and toluene resulted in a significant improvement in reaction profile. To test the hypothesis, the introduction of t-amyl alcohol to the toluene route significantly deteriorated the LC-MS profile of the reactions with more hydrolysis products evident.

Biomedical applications

The LC-MS technique is useful for the detection of steroid drugs in body fluids and in profiling endogenous steroids. Steroid sulphates have been detected with high sensitivity using this method. Plasmaspray has been used to test saliva for steroid hormones in patients suffering from congenital adrenal hyperplasia. Amino acids were one of the first compounds analyzed using LC-MS coupled with laser desorption and thermospray. Nucleosides, nucleotides, saccharides, peptides, and proteins were all analyzed and their molecular weights were determined using LC-MS coupled with electrospray. Bile acids have also been determined using LC-MS and thermospray. Ultra-pure additives and solvents such as acetic acid, acetonitrile, ammonium acetate, ammonium bicarbonate, ammonium fluoride, and ammonium hydroxide are available from Sigma Aldrich for use in LC-MS systems.

Environmental applications

LC-MS is used in the analysis of diverse samples such as soil, drinking water or waste water, air, and sludge. The samples may belong to many

different chemical species ranging from non-polar hydrocarbons to ionic organometallic species. Several pesticides and herbicides including triazine derivatives, chlorophenols, phenoxy alkanoic acids, and sulfonylurea herbicides can be analyzed using LC-MS. Separation of polycyclic aromatic hydrocarbons and organometallic compounds is also possible using the technique.

Biochemical screening for genetic disorders

Blood samples of new born babies are analyzed using LC-MS to detect metabolic disorders. Second-tier LC-MS testing has been used for confirming the results of first-tier immunoassays in new born screening.

Pharmaceuticals

LC-MS is widely used in the determination of pharmaceutical compounds and especially in the separation of optically active drugs. Antibiotics and potential anti-malarials have been studied using thermospray. The use of LC-MS in the identification of bromazepam and similar drugs in case of intoxication has been successfully demonstrated. Detection, isolation, and purification of drug metabolites is another major application of LC-MS, as they are chemically or thermally labile, and need liquid chromatography. Separation and characterization of components in a crude mixture of natural products such as complex lipids, alkaloids, and hydroxylated or unsaturated fatty acids has been achieved using LC-MS. LC-MS systems from Shimadzu feature high sensitivity, provide precise quantification, and improve analytical throughput in food, pharmaceutical, chemical, and environmental analysis.

Therapeutic drug monitoring and toxicology

In drug monitoring, LC-MS assays have been developed for immunosuppressants including tacrolimus, cyclosporin, everolimus, sirolimus, and mycophenolic acid. Similar assays for aminoglycosides, anticancer drugs, and antiretrovirals have also been described. LC-MS assays can be multiplexed to measure several drugs and metabolites in a single run, thus simplifying lab workflows and providing additional information such as metabolite profiles in clinical biochemistry labs. LC-tandem MS is used in toxicology screening for the detection of a wide range of toxins, drugs, and metabolites. Thermo Fischer provides a range of LC-MS systems including ion trap LC-MS, triple and single quadrupole LC-MS solutions. This is in addition to LC-MS software and accessories suitable for the analysis of environmental pollutants, complex proteins, and drug metabolites.

Steroid hormones

LC-MS analysis has been helpful in steroid biochemistry studies where traditional immunoassays have not proved very effective. Highly sensitive LC-MS assays have been developed for the measurement of low dihydrotestosterone and testosterone levels in women and children. Urinary steroid profiling has been simplified using LC-MS methods as these steroids are excreted as glucuronide or sulfate conjugates which will need to be hydrolyzed and derivatized for GC-MS analysis.

Vitamins and related metabolites

LC-MS is a preferred method for the measurement of vitamin D and its metabolites. LC-MS assays have been developed for 25-hydroxyvitamin D_2 and D_3 in plasma and serum. Similar assays are also available for fat-soluble vitamins such as vitamin K_{15} and vitamin $E_{13,15}$.

Application of LC/ESI-MS in forensic sciences

LC-MS is used for determination of toxicity, in drug analysis and also in trace analysis. By using small amount of sample, the toxins in different material can be determined with LC-MS. Any toxic metabolites in food or beverages can be determined by using LC-MS.

Bioavailability and bioequivalence study

Comparative bioequivalence studies in which quantitative determination of drugs or metabolites is measured in biological matrix, pharmacodynamics, clinical trials and *in-vitro* dissolution tests.

Determination of molecular weights

LC-MS is used for determination of molecular weights of known and unknown compounds. It provides the information about molecular weight, structure, identification, quantity of sample components. LC-MS is used for determination of molecular masses of proteins, nucleic acids, polymers and peptides.

Determination of assay of drug and intermediates

LC-MS is used in pharmaceutical industry for determination of assay of drug substances, drug products, intermediates and their related compounds.

Agrochemical and pesticides industry

It is used in determination of different components present in the fertilizers and pesticides.

Molecular pharmacognosy

LC-MS determines the contents and categories of different groups of cultured plant cells and select the pair of groups with the biggest different content of ingredient for the study ingredient difference phenotypic cloning.

Characterization and identification of compounds

Like carotenoids, proteomics, products of degradation etc.

Future prospects of LC-MS

Metabolomics

At present, mass spectrometry (MS) based metabolomics has been widely used to obtain new insights into human, plant, drug and biomarker discovery, nutrition research, food control and microbial biochemistry. The next 5–10 years will inevitably witness increased inter-laboratory cooperation in order to collate as much LC-MS based metabolite data as possible. In-house MS/MS libraries will likely become more available to interested collaborators with similar model samples and instrumentation, increasing the knowledge base of all participating laboratories. The integration of NMR to LC-MS-based metabolic profiling and metabolomic studies will likely increase, either through the offline analysis of collected LC fractions or through hybrid LC-NMR-MS instrumentation.

In contrast, GC-MS is unlikely to become an integrated component to an LC-MS strategy, due to the fundamental differences in the two techniques and the inherent difficulty in utilizing such complementary information for unknown biomarker characterization. However, GC-MS will remain a tool for quantifying those metabolites not amenable to LC-MS analysis due to relatively poor ionization efficiencies. New informatics tools for the combined automated generation of candidate empirical formula and stereoisomer generation for detected metabolite features may become available, as well as algorithms designed to predict the chemical structure of unknown metabolites based on CID MS/MS fragmentation spectra. It has been more positive for MS-based metabolomics that the number and quality of spectral databases has increased more significantly over the past 5 years. However, this growth creates other problems that need to be addressed soon to allow for palpable progress in metabolomics. Two major issues are conspicuous, which could be best addressed by coordinated and unified actions in future.

Proteomics

The spectacular development of instrumentation for LC-MS of peptides over the last decade has almost left protein sample preparation, including

extraction and digestion, as the one major critical point in proteomic workflows in the overall performance of proteomic experiments. Cleanness of samples in relation to non-protein contaminants dramatically affects the protein identification rate. The current trend in simplifying sample preparation steps and handling minimal quantities of biological material has led to the integration of protein extraction, digestion, and fractionation in a single pipette tip that holds a small disk of membrane-embedded separation material, the so-called StageTip. Extrapolating these protocols to plant material is challenging given protein scarcity and the abundance of interfering compounds in plant cells, but it is an exciting challenge because the benefits for research of SM will outweigh development efforts.

Pharmacovigilance

Pharmacovigilance (PV or PhV), which is referred to as Drug Safety. It is one of the pharmacological sciences which relates to the collection, detection, assessment, monitoring, and also prevention of adverse side effects with pharmaceutical products. The detection and monitoring can be done by LC-MS based disease modifying technique which provides detailed profiles.

Organic/inorganic hybrid nanoflowers

Analytical method of LCMS can be employed for the detection of General nanoflowers. It helps in the development of drug delivery systems, biosensors, biocatalysts, and bio - related devices is anticipated to take multiple directions. New synthesis principles, new types of hybrid nanoflowers, and detailed mechanisms are expected to emerge. The application of nanoflowers in bio-catalysis and enzyme mimetics, tissue engineering, and the design of highly sensitive bio-sensing kits, as well as industrial bio-related devices with advanced functions, various and controllable syntheses, biocompatibility, and modifications of hybrid nanoflower structures and properties, should receive increasing attention.

Advantages of LC-MS combination

It is one of the most powerful analytical tools for organic compound analysis. The key advantages of LC-MS Method over HPLC Methods includes.

1) Selectivity-co-eluting peaks can be isolated by mass selectivity and are not constrained by chromatographic resolution.
2) Peak assignment-A chemical finger print for the compound of interest generated ensuring correct peak assignment in the presence of complex matrices.

3) Molecular weight information-confirmation and identification of known and unknown compounds.

4) Structural information-controlled fragmentation enables structural elucidation.

5) Rapid method development-provides easy identification of elucidated analytes without retention time validation.

6) Sample matrix adaptability-decreases sample preparation time.

7) Quantitation-quantitative and qualitative data can be obtained easily with limited instrument optimisation.

Disadvantages

1) Expensive.

2) Not portable.

3) Requires an experienced technician.

4) Moderate through put.

E.g.: If you want to analyse, for example 1,00,000 samples by LC-MS, it would probably take about a year depending on how fast the run time were through put does not matter if you are only analysing 5-10 samples, but in drug screening where the analysis of thousands of samples is in routine, it can be a major limitation.

Conclusion

Rapid liquid chromatography-tandem mass spectrometry plays an important role in both preclinical development and clinical trials. Based on the papers published in English, the assay run times of rapid LC-MS/MS methods for a single analyte and multiple analytes were identified as 4 and 6 min, respectively. With the development of UPLC systems and the availability of more isotopically-labelled internal standards, assay run times for rapid analysis of anticancer drugs/metabolites could be further reduced in order to accelerate drug development.

Currently, LC-MS/MS has been widely used to investigate pharmacokinetics of oncology drugs to support early phase clinical trials and determine potential drug-drug interactions. The advantage in using LC-MS/MS is its super sensitivity and specificity, which makes it a powerful tool for clinical therapeutic monitoring of oncology drugs. The LC-MS is a hyphenated technique used in combination with separation power of HPLC with detection power of Mass spectrometry. It is widely used in pharmaceutical, chemical, food, agrochemical industries, environmental and

forensic applications. LC-MS is used for qualitative and quantitative determination of drug substances and biological samples. Also, it is commonly used in drug research and quality control.

Liquid Chromatography Mass Spectrometry (LC-MS) is an analytical technique that couple's high resolution chromatographic separation with sensitive and specific mass spectrometric detection. It is an efficient analytical technique for *in-vitro* determination of drug metabolites, in new drug discovery, screening of plant constituents, analysis and identification of impurities and degradation products in pharmaceuticals. Advancement in LC-MS technique can be successfully implemented for separation and identification of analyte ions.

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